Final Public Review Draft

Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

June, 2001

Acknowledgements

The following OEHHA staff participated in developing this document

Joe Brown, Ph.D.
John Budroe, Ph.D.
James Collins, Ph.D.
Stan Dawson, Ph.D.
Daryn Dodge, Ph.D.
Richard Lam, Ph.D.
David Lewis, Ph.D.
Michael Lipsett, M.D.
Melanie Marty, Ph.D.
Tom MacDonald, Ph.D.
Mark Miller, M.D.
David Morry, Ph.D.
Bart Ostro, Ph.D.
Judy Polakoff, M.S.
Pierre Raymond, Ph.D.
Andrew Salmon, Ph.D.
Bruce Winder, Ph.D.

In addition, the following contractors were used to help develop our focused literature reviews:

Dr. Michael Colllins, University of California, Los Angeles
Dr. Joe Landolph, University of Southern California
Dr. Thomas Meehan, University of California, San Francisco
Dr. Allan Smith, University of California, Berkeley

Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act

I. Introduction

In recent years, there have been growing concerns regarding children's environmental health, especially in recognition of children's potentially increased susceptibility to environmental contaminants. Because of these concerns, the California Legislature passed the Children's Environmental Health Protection Act (SB 25, Escutia; chaptered 1999), which requires the California Environmental Protection Agency to specifically consider children in setting Ambient Air Quality Standards and developing criteria for Toxic Air Contaminants (TACs). The Office of Environmental Health Hazard Assessment (OEHHA) is responsible for evaluating health effects information on the criteria air pollutants: ozone, carbon monoxide, sulfur oxides, nitrogen oxides, particulate matter, hydrogen sulfide, sulfates, and lead. OEHHA also provides health-based recommendations for Ambient Air Quality Standards (AAQS) for these compounds to the Air Resources Board (ARB) which sets the standards. In addition, OEHHA is responsible for conducting health effects assessments of TACs which are provided to the ARB for use in risk management activities. The new legislation requires OEHHA to consider in its health effects assessments and recommendations: (1) exposure patterns among infants and children that result in disproportionately high exposure; (2) special susceptibility of infants and children; (3) effects of simultaneous exposures to compounds with the same mechanism of action; and (4) any interactions of air pollutants. The law requires OEHHA to evaluate available information on the TACs and develop a list of up to five TACs that "may cause infants and children to be especially susceptible to illness" by July 1, 2001. The purpose of this document is to describe the prioritization procedure used to develop the initial listing. The list is to be updated periodically.

While the statute requires OEHHA to evaluate infants and children issues specifically, it is important to note that existing risk assessment methodologies use protective assumptions to protect children when evaluating and quantifying risk from exposure to chemicals. These assumptions include use of the 95% Upper Confidence Limit of the slope of the dose-response curve when evaluating cancer potency and use of an uncertainty factor of 10 for interindividual variability in the human population when developing noncancer Reference Exposure Levels. Risk assessors have always known that such assumptions are crude but data have generally been

lacking to use anything other than such assumptions for most chemicals. As part of the long-term goals of SB 25, OEHHA will be evaluating available information to assess the adequacy of these assumptions in protecting infants and children from toxic air contaminants.

This document first presents OEHHA's prioritization of the identified toxic air contaminants for the purpose of developing the list of TACs under SB 25 (Section II. A.). We describe particular toxicological endpoints of concern for infants and children and the why these endpoints are important (Section II.B.) We then describe the listing under SB 25 and include a second tier of chemicals of concern but which did not merit placement in the top 5 at this time (Section II.C.). The document then provides an introduction to the factors that influence the body's responses to environmental contaminants and other toxicants and which differ between children and adults (Section III). This section is not meant to be exhaustive; rather it provides an introduction to the issues that should generally be considered, if data are available, when assessing impacts on infants and children. Finally, summaries of TACs that were candidates for listing under SB 25 in the first list of five are provided in Appendix C.

It should be noted that OEHHA is precluded from evaluating "pesticides in their pesticidal use" for listing under SB 25. There are several pesticides that are TACs and whose mechanism of toxicity would suggest consideration for listing. However, SB 25 reiterated and confirmed previous statutory provisions specifying that pesticides in their pesticidal use are outside the purview of OEHHA and ARB in administering the Toxic Air Contaminant Program (Health & Safety Code Sections 39655 and 39660). Nonetheless, OEHHA was able to consider methyl bromide, a pesticide, for listing pursuant to SB 25. An appellate court decision (Harbor Fumigation, Inc. v County of San Diego Air Pollution Control District) held that emissions of methyl bromide from fumigation chambers is **not** a pesticide in its pesticidal use. Rather, it is only a pesticide in its pesticidal use while inside the fumigation chamber. The court held that once the use of a pesticide is completed and its waste gas emitted into the ambient air from the facility, then it is subject to the general Toxic Air Contaminant regulatory regimen. Thus, such emissions are properly subject to ARB and Air District regulation, as well as review under SB 25.

In addition, OEHHA would like to note that there are many studies linking environmental tobacco smoke (ETS) exposure to poor health outcomes in exposed children. OEHHA reviewed the health effects of ETS in the document entitled " Health Effects of Exposure to Environmental Tobacco Smoke", published as a National Cancer Institute Monograph (NCI, 1999). ETS is associated with adverse health effects in infants and children including reduced birth weight, intrauterine growth retardation, increased risk of sudden infant death syndrome, exacerbation of asthma and induction of new asthma, chronic respiratory symptoms, increased lower airway infections, and acute and chronic otitis media. (Some of the studies with ETS include data associating some of these outcomes with the PAH component of ETS and are described in Appendix C, PAH summary.) It is estimated that ETS-related exacerbation of asthma affects up to 120,000 children in California annually, that ETS-related otitis media may result in 78,000 to 188,000 doctor visits per year among children under age 3, that from 18,000 to 36,000 cases of ETS-related bronchitis or pneumonia can be predicted to occur in children younger than 18 months, and that from 960 to 3120 new cases of asthma in California per year may be attributable to ETS exposure (NCI, 1999). Since ETS has not been identified as a Toxic Air Contaminant , OEHHA is precluded from listing ETS as a TAC that may cause infants and children to be especially susceptible to illness at this time. However, the ARB has entered ETS into the identification phase of the Toxic Air Contaminant program. Since SB 25 requires consideration of infants and children's health impacts in evaluating candidate TACs, the evaluation of ETS will primarily focus on these adverse health impacts in infants and children.

II. Initial prioritization of all TACs

A. Selection for Focused Literature Review

OEHHA developed a system of prioritizing TACs to assist in identifying up to five substances which posed a potential hazard to children in California. We began with the entire list of over 200 identified TACs and prioritized them based on their toxicity and extent of air emissions or measured ambient concentrations in the state. We then chose 36 chemicals for focused literature reviews. Based on the strength of the toxicity data for the TACs and extent of exposure, we narrowed the list to 17 TACS and provide summaries of those TACs in Appendix C of this document. We also choose five of those TACs for the initial listing under SB 25, which we are

statutorily mandated to complete by July 1, 2001. There have been three Panel meetings at which the document was discussed. Transcripts are available on the ARB website (www.arb.ca.gov). These discussions indicated that the initial proposed list of five (Tier 1) was likely to change. It is also important to stress that we believe some of the other TACs pose a threat to infants' and children's health and need to be evaluated in future updates of the list; however, the statute precludes us from listing more than five by July 1, 2001. We provide in the final document a list of the five that will constitute the initial list of TACs that may cause infants and children to be especially susceptible to illness, as well as a second list of TACs for which there are concerns about impacts on infants and children. The following is a summary of the steps taken in the prioritization.

1. We began with the compound summary table from the ARB document entitled Toxic Air Contaminant Identification List Compound Summaries (CARB, 1997), which lists all TACs with data on ambient air concentrations and chronic Reference Exposure Levels (RELs). (A chronic REL is an airborne concentration at or below which adverse noncancer health impacts would not be anticipated.) This table originated from the prioritization of TACs for health effects review conducted by the Air Resources Board. The ARB prioritization process was endorsed by the state's Scientific Review Panel on Toxic Air Contaminants. We updated this information with more recent data on ambient air concentrations in California from the ARB's monitoring network. For those chemicals lacking recent California monitoring data, we used the older monitoring data that were in the original ARB summary table. It should be noted that for a number of these compounds, there are no California-specific data. Ambient concentration data reported in the original ARB table that were not from the ARB's monitoring efforts were retained for our purposes. These data came from a compilation of measurements published by the U.S.EPA (Ambient Concentration Summaries for Clean Air Act Title III Hazardous Air Pollutants, 1993). Means of the U.S.EPA-compiled data reported in the table may be from one location, more than one location, and from measurements conducted in different years (many in the 1970s and 1980s). Thus, the data are uncertain in terms of representativeness for chronic exposures and in terms of applicability to California. Nonetheless, the data do provide some information on potential exposures.

2. We divided the ambient air concentration by the chronic REL, which provided a noncancer score. Where chemicals did not have an approved chronic REL, we utilized a proposed chronic REL or a previously utilized REL from CAPCOA (1993). This provided us with a score for the chemicals for noncancer toxicity combined with exposure potential.

3. For the carcinogens, we multiplied the cancer unit risk factor by the ambient air concentration. (A cancer unit risk factor describes the additional risk of cancer associated with inhaling air containing one microgram of a specified carcinogen per cubic meter.) This provided an estimate of the cancer risk posed by the carcinogenic TACs.

4. The noncancer and cancer risk scores appear in Table 1A (chemicals chosen for focused literature review) and 1B (chemicals not chosen for focused literature review) for each chemical in alphabetical order. Note that a high noncancer hazard quotient (ambient concentration divided by chronic REL) would suggest further review. Similarly, a high cancer risk estimate (ambient concentration X unit risk factor) would also suggest further review. This process provided a ranking based on existing health criteria and ambient air concentration data, but did not necessarily include information on differential sensitivity of infants and children. This is because the chronic RELs may or may not have been based on an endpoint for which concern would be raised with regard to infants and children as a more sensitive subpopulation. In addition, not all TACs have been measured in ambient air. Thus, other factors noted in Step 5 were considered during the prioritization. This resulted in the consideration of additional TACs for listing; these TACs are included in Table 1A or 1B but have no cancer or noncancer ranking available.

5. The entire list of TACs (Appendix A, Table A), not just those with existing ambient air concentration data, was reviewed to identify any chemical that should obviously be considered for listing based on existing knowledge of the toxicity. In particular, we were looking to see if any of these chemicals induced a toxicological endpoint associated with possible increased susceptibility in a developing organism (i.e., neurotoxicity, immunotoxicity, endocrine toxicity, respiratory toxicity, or developmental toxicity: see Section II.B-D.). We also examined emissions inventory data from the Air Toxics Hot Spots program to estimate the extent of

emissions from stationary sources in California (1998 data). In this process we identified chemicals for further review (Table 1A) and those of lower priority for which further review would be deferred (Table 1B). Tables 1A and 1B note whether the California emissions data were low, moderate, high or very high and whether California hot spots emissions were a factor in pursuing a focused literature review on those chemicals at this time. Table B in Appendix A contains the TACs that were screened out at this initial stage and indicates whether they were missing ambient air data, CRELS or unit risk factors.

Thirty-six TACs were chosen for focused literature reviews based partly on the ranking process (described in steps 1-4), partly on known emissions information, and partly on the known toxicological endpoints of the chemicals (e.g., developmental neurotoxicity for mercury and lead) (Table 1A).

Our ability to conduct focused reviews was limited by available resources; this impacted the number of TACs we could evaluate in this first prioritization. Focused literature reviews for the 36 TACs were developed in order to identify the information that may be most pertinent to the question of whether infants or children may be more sensitive or susceptible to those chemicals than adults. The literature reviews were conducted both in house and via contract with UCLA, UCB, UCSF, and USC (see acknowledgements page) .

6. Based on the information gathered during the focused literature reviews, we chose eleven potential candidates for the initial listing of up to five TACs that may cause infants and children to be especially susceptible to illness. In addition, 6 more chemicals were added upon request of the Scientific Review Panel. At this stage, this decision was heavily influenced for some of the compounds by the extent of information indicating differential toxicity and adverse consequences for infants and children relative to adults and less so by the estimated exposures to the compounds. For example, while there may be exposures to some compounds which have limited evidence of differential susceptibility of infants and children (e.g., methanol), other compounds may have more limited exposure but extremely strong evidence of differential effects (e.g., lead, mercury, noncoplanar PCBs, dioxins, vinyl chloride). For the purposes of developing the initial SB 25 list, we chose to look closely at those compounds with stronger evidence of differential susceptibility of infants and children. As such, we weighted studies looking at

toxicological endpoints heavily. We feel this is warranted for this first round of listing under the statute due to the constraint of listing only up to 5 TACs by July 1, 2001. This initial list does not imply that other TACs are of little or no concern. Instead, this review focused on those chemicals that have more compelling toxicity data. Thus some of the 17 chemicals presented in Appendix B have relatively higher exposures than others, but those with lower exposures have very compelling toxicity and epidemiology data indicating more adverse effects from exposure in infants and children than in adults. Table 4 contains a listing of the 17 TACs, and indicates which chemicals we chose to list under SB 25 (Tier 1), and which chemicals are of concern but do not make the first list of five (Tier 2).

The list of TACs that "may cause infants and children to be especially susceptible to illness" must be updated pursuant to the statute by July 1, 2005 (although we are not precluded from updating sooner). We will be conducting further evaluations of TACs over the next few years. This will include an evaluation of criteria for the use of supporting and mechanistic information as a basis for listing.

In evaluating the information obtained during the focused literature reviews for each of the 36 TACs in order to decide whether the TAC merited consideration for placement on the first list of five TACs (step 6 above), we used the following criteria as a guide:

1. Any evidence indicating that infants and children may be more susceptible than adults to the toxicological effects associated with that TAC. The strength of this evidence was weighted heavily in this initial selection of 17 TACs that disproportionately impact children.

2. The nature and severity of the effect(s), especially irreversible effects.

3. Any evidence indicating that, based on current risk assessment methodology, the existing health criteria may not be adequately protective of infants and children.

4. Any potential difference in susceptibility of infants and children relative to adults to carcinogenesis based on known information or plausible mechanisms.

5. Extent of exposure and/or the magnitude of risk estimated to occur at concentrations typical of California urban ambient air, and any indication that infants and children may be more heavily exposed to materials contaminated by airborne particles (e.g., housedust).

Table 1A TACs that were chosen for focused literature review; noncancer and cancer risk estimates and reason for conducting literature search.

SUBSTANCE	Ambient Air Conc.(µg/m^3) most recent [1]	Ambient Conc./REL	Unit Risk Factor X ambient air conc.	Reasons for Conducting Literature Search
Acetaldehyde	**1.980**	0.2	5.3E-06	Respiratory irritant; possible asthma exacerbation; high California hot spots and mobile source emissions; secondary formation in atmosphere.
Acrolein	(14.3)* 0.15	(238)* 2.5		Conc. above cREL; respiratory irritant; asthma exacerbation; moderate California hot spots emissions
Arsenic and compounds	**.0015**	0.05	5E-06	Developmental toxicity (perinatal mortality); human carcinogen; moderate California hot spots emissions
Asbestos				Recent studies of mesothelioma in environmentally exposed populations; concern about environmental exposures including school premises.
Benzene	**1.978**	0.03	5.9E-05	Hematotoxicity, leukemia; high California hot spots and mobile source emissions
Benzo[*a*]pyrene and other PAHs	**.0002** (B[*a*]P only)		2.2E-07	Carcinogen, developmental toxicity; immunotoxicity; indoor, moderate California hot spot emissions; mobile source emissions
Butadiene (1,3-)	**.442**	.02	8E-05	Developmental toxicant; multisite carcinogen; moderate California hot spots emissions
Cadmium and compounds	**.000411**	0.02	1.8E-06	Nephrotoxicity; possible developmental toxicity
Carbon disulfide				Neurotoxicity;
Carbon tetrachloride	.693	0.02	2.9E-05	Developmental and neurotoxicity
Chlorine	**1.490 ** (particulate Cl)**	0.007**		Respiratory irritant; possible asthma exacerbation; high California hot spots emissions
Chromium VI	**.00011**	.00055	1.9E-05	Potent human carcinogen
Dichlorobenzene (1,4-) (p-Dichlorobenzene)	.720	.0009	7.9E-06	Neurotoxicity; respiratory irritant; household exposures; moderate California hot spots emissions

SUBSTANCE	Ambient Air Conc.(µg/m³) most recent [1]	Ambient Conc./REL	Unit Risk Factor X ambient air conc.	Reasons for Conducting Literature Search
Diesel Exhaust PM	1.800 [3]	0.4	5.4E-04	Enhancement of respiratory allergy; possible asthma exacerbation; Carcinogen; high mobile source emissions.
Formaldehyde	3.19	1.1	1.9E-05	conc. near cREL, respiratory irritant; asthma exacerbation; carcinogen; very high California hot spots and mobile source emissions; secondary formation in atmosphere;
Glycol ethers				Developmental toxicity; high California hot spot emissions
Hexane (n-)				Neurotoxicity; high California hot spot emissions
Lead [5]				Well-characterized human developmental neurotoxin; high California hot spot emissions.
Manganese compounds	.020	0.1		Neurotoxicity; high California hot spots emissions
Mercury	.0016	0.02		Well-characterized human developmental neurotoxin; some hot spots emissions; high exposures from fish, but low air exposures; moderate California hot spots emissions.
Methanol	23.100	0.006		Developmental toxicity, very high California hot spots emissions
Methyl bromide (Bromomethane)				Neurotoxicity, potential developmental toxicity; moderate California hot spot emissions
Methyl chloroform (1,1,1-Trichloroethane)	.482	0.0005		Neurotoxicity; very high California hot spots emissions; may appear in consumer products.
Methyl ethyl ketone				Potential increased usage due to exemption as VOC; high California hot spots emissions
Methylene chloride (Dichloromethane)	2.155	0.005	2.2E-06	Metabolized to CO; very high California hot spots emissions; carcinogen
Naphthalene				Included w/PAH ;Carcinogen, developmental tox.; high California hot spots emissions
Nickel and compounds	.0034	0.07	8.8E-04	Immunotoxicity; asthma, carcinogen; high California hot spots emissions.
Phosphine	.0386	0.1		Potent toxin; hemolytic poison
Polychlorinated biphenyls (PCBs)				Human dev neurotoxicity, endocrine toxicity. Exposures may exceed effect threshold. Bioaccumulates.
Propylene oxide				High California hot spots emissions

SUBSTANCE	Ambient Air Conc.(µg/m^3) most recent[1]	Ambient Conc./REL	Unit Risk Factor X ambient air conc.	Reasons for Conducting Literature Search
Styrene	**.340**	.0004		Very high California hot spots emissions; neurotoxicity
Tetrachlorodibenzo-p-dioxin (2,3,7,8-) and related dioxin and dibenzofuran congeners				Potent immunotoxicity, developmental and endocrine toxicity, carcinogen. Exposure exceeds effect threshold. Bioaccumulates: air is an important transport medium.
Tetrachloroethylene (Perchloroethylene)	**.747**	0.02	4.4E-06	Carcinogen; very high California hot spots emissions
Toluene	**7.526**	0.025		Developmental tox; very high California hot spots emissions
Toluene diisocyanate (2,4-) and other diisocyanates.				Potent respiratory irritants and sensitizers; moderate California hot spots emissions.
Vinyl chloride				Increase in potency w/early exposures; moderate California hot spots emissions.
Xylenes (isomers and mixtures)	**4.465**	0.006		Respiratory irritant; very high California hot spots emissions

1. Based on the year for which the most recent data are available: 1997, 1998 or 1999; numbers in bold are data from the California Air Resources Board. Other numbers are from various sources (as compiled in U.S. EPA, 1993);
   * parenthetical concentration based on U.S.EPA compilation, 1993; value of 0.15 based on USEPA cumulative exposure project modeling California.
   ** ambient measure is of total particulate Cl. Assuming 0.1% of this is chlorine (although ARB estimates it is probably zero), then a ratio of ambient to cREL would be about 0.007
2. Emissions data based on Air Toxics Hot Spots Stationary Source Emissions Database (ATEDS); low emissions means <10,000 pounds per year statewide from all facilities in ATEDS database; moderate means 10,000 to <100,000 lbs/yr; high means 100,000 to <1,000,000 lbs/year; very high means ≥ 1,000,000 lbs/year.
3. Estimated outdoor diesel exhaust PM10 air concentration for California, year 2000
4. IARC lists whole diesel exhaust as 2A
5. Lead was initially to be evaluated as a criteria air pollutant. However, it was decided to evaluate it as a TAC because most of the concerns are from site-specific emissions rather than average ambient concentrations.

Table 1B. TACs that were not chosen for focused literature review; noncancer and cancer risk estimates and reason for deferring literature search.

SUBSTANCE	Ambient Air Conc.(µg/m^3) most recent [1]	Ambient Conc./REL	Unit Risk Factor X ambient air conc.	Reasons for Deferring Literature Search [2]
Acrylamide				Low California hot spots emissions
Acrylonitrile	.660	0.3	1.9E-04	Low California hot spots emissions
Ammonia				Low toxicity and low ambient; although concern about California hot spots emissions
Aniline	1.300		2.1E-06	No known California hot spots emissions
Benzidine				No known California hot spots emissions
Benzyl chloride				Low California hot spots emissions
Beryllium compounds	.000019	0.02	4.6E-08	Low California hot spots emissions
Bis(2-ethylhexyl)phthalate (DEHP)				Low California hot spots emissions; no cREL adopted.
Chlordane	.038		1.3E-05	Banned pesticide; no known California hot spots emissions
Chlorobenzene	.270	.0003		Low California hot spots emissions but some concern
Chloroform	.185	0.0006	9.8E-07	Low California hot spots emissions; some concern for developmental tox and carcinogenicity.
Chloroprene	.290	0.3		Low California hot spots emissions
Copper compounds	.033	0.014		Low toxicity; low California hot spots emissions; beneficial at low doses (essential element).
Cresols/Cresylic acid (isomers/mixtures)				Moderate California hot spots emissions
DBCP (1,2-Dibromo-3-chloropropane)	.100	0.5	2E-07	Banned pesticide, no known California hot spots emissions
DDE	.0045		4.4E-07	Metabolite of banned pesticide.
Dichlorvos	.0032		2.7E-07	pesticide
Dimethyl sulfate	7.400		3.0E-02	Ambient data uncertain; low California hot spots emissions

SUBSTANCE	Ambient Air Conc.(µg/m^3) most recent [1]	Ambient Conc./REL	Unit Risk Factor X ambient air conc.	Reasons for Deferring Literature Search
Dioxane (1,4-) (1,4-Diethyleneoxide)	.440	.00015	3.4E-06	Low ambient concentration
Epichlorhydrin (1-Chloro-2,3-epoxypropane)				Low California hot spots emissions
Ethyl acrylate				Low California hot spots emissions
Ethyl chloride (Chloroethane)	**55.700**	0.002		Low toxicity
Ethylene dibromide (Dibromoethane)	**.040**	0.05	2.8E-06	No longer used as gasoline additive or as fumigant
Ethylene dichloride (1,2-Dichloroethane)	**.400**	0.001	8.8E-06	Moderate California hot spots emissions; moderate toxicity; some concern for carcinogenicity.
Ethylene oxide				Low California hot spots emissions but some concern re hot spots
Ethylidene dichloride (1,1-Dichloroethane)	.170		2.7E-07	Low California hot spots emissions; no cREL
Gasoline vapors				Major components considered
Glutaraldehyde				Moderate California hot spots emissions
Heptachlor	.007		1.1E-05	Banned pesticide; no known California hot spots emissions
Hexachlorobenzene	.00021	0.00008	1.1E-07	No known California hot spots emissions
Hexachlorocyclo-pentadiene				No known California hot spots emissions
Hexachloroethane	.010		1.1E-07	No known California hot spots emissions
Hydrazine				Low emissions; some concern re California hot spotsemissions
Hydrochloric acid				Concern about California hot spot emissions; but T1/2 low
Hydrogen fluoride (Hydrofluoric acid)	3.400	0.1		Concern, but ambient data uncertain. Toxicity shows threshold, beneficial effect at lower doses.
Hydrogen selenide				No known California hot spots emissions
Hydrogen sulfide				Criteria air pollutant

SUBSTANCE	Ambient Air Conc.(µg/m^3) most recent [1]	Ambient Conc./REL	Unit Risk Factor X ambient air conc	Reasons for Deferring Literature Search [2]
Lindane (and other isomers of hexachlorocyclohexane)	.00023	.0002	7.1E-08 (Lindane): 2.5E-07 (HCH)	Low California hot spots emissions, pesticide (most uses cancelled).
Maleic anhydride				Low California hot spots emissions
Methyl isocyanate				No California hot spots emissions data; principal source in CA is from pesticidal use of Metam Na; short T1/2; but toxicity concern (respiratory irritant, immunotoxicity)
Methyl methacrylate				Low tox; low California hot spots emissions
Methylenedianiline (4,4')				Low California hot spots emissions
Nitrobenzene	.610	0.4		Ambient data uncertain; low California hot spots emissions
Nitropropane (2-)				Low California hot spots emissions
N-Nitroso-dimethylamine	2.400		1.2E-02	Ambient data uncertain; low California hot spots emissions
Pentachlorophenol	.0009		4.6E-09	No known California hot spots emissions; low ambient conc
Phenol	.030	.0002		Low ambient concentration
Phthalic anhydride				Moderate California hot spots emissions
Propylene dichloride (1,2-Dichloropropane)	.750		1.7E-05	No known California hot spots emissions; ambient data uncertain
Selenium compounds	**.0011**	0.00005		Moderate California hot spots emissions; low ambient concentration
Sodium hydroxide				Short T1/2
Tetrachloroethane (1,1,2,2-)	.500		2.9E-05	Low California hot spots emissions
Trichloroethane (1,1,2-) (Vinyl trichloride)	.300		4.8E-06	Moderate California hot spots emissions; no cREL
Trichloroethylene	**.167**	.0003	3.3E-07	Low ambient concentration
Trichlorophenol (2,4,6-)	.300		6.0E-06	No known California hot spots emissions
Vinylidene chloride (1,1-Dichloroethylene)				Low California hot spots emissions

SUBSTANCE	Ambient Air Conc.(µg/m^3) most recent [1]	Ambient Conc./REL	Unit Risk* Factor X ambient air conc.	Reasons for Deferring Literature Search [2]
Zinc compounds	**.047**	0.0013		Low toxicity; low California hot spots emissions; beneficial at low doses (essential element).

1.Based on the year for which the most recent data are available: 1997, 1998 or 1999; numbers in bold are data from the California Air Resources Board. Other numbers are from various sources (as compiled in U.S. EPA, 1993)

2.Emissions data based on Air Toxics Hot Spots Stationary Source Emissions Database (ATEDS); low emissions means <10,000 pounds per year statewide from all facilities in ATEDS database, moderate means 10,000 to <100,000 lbs/yr; high means 100,000 to <1,000,000 lbs/year; very high means ≥ 1,000,000 lbs/year.

B. Critical Systems and Periods in Development

Certain systems have critical periods during their development when they are particularly vulnerable to lasting injury by xenobiotic chemicals or other agents. Among these critical systems are the three information processing systems of the body: the central nervous system, the endocrine system, and the immune system. Xenobiotic chemicals can interfere with programming of these critical systems. Each of these complex systems is programmed as it develops. The central nervous system is programmed to recognize and respond to internal and external stimuli in an adaptive manner that supports the survival of the organism. The endocrine system is programmed to provide signals to the various organ systems enabling them to coordinate their development - not only during early childhood, but also during puberty. The immune system is programmed to distinguish self from nonself, and to respond to nonself antigens in a measured manner in order to combat infection or the emergence of potentially malignant cells. In developing and in mature organisms these three systems work together to control and protect the organism. Effects on one of these systems can be expected to have collateral effects on the others.

The respiratory system is also a critical system because, although fully functional at birth, it undergoes significant development in the first years of life. As with the three information processing systems, interference with the developing respiratory system can have consequences that last a lifetime.

Because these organ systems have long developmental periods and are known to be irreversibly impacted by specific toxicants, any toxicological or epidemiological information indicating impacts on these systems was considered a red flag. We are taking a close look at chemicals that impact these systems in evaluating TACs for listing under SB 25.

1. Developmental Toxicants and the SB 25 List

Developmental toxicants can induce effects that are irreversible and may act on developmental events that occur prenatally, postnatally, or both. Many of these effects are produced in animals

and humans without maternal toxicity. Development is a continuum that starts at conception and continues through adolescence. Indeed, even preconceptual exposures have induced effects in the offspring presumably by altering germ cells.

Chemicals may produce a range of developmental effects at different dose levels and periods of development and durations of exposure. For example, lead exposure results in toxicity to the nervous system following prenatal exposure and also when exposure occurs postnatally and during childhood (Thacker et al., 1992; Needleman et al., 1979). Chemicals that are teratogenic may also induce other toxicological effects. Because of the varying effects and timing of sensitivity for developmental toxicity, and a general lack of information on all developmental windows of susceptibility that may be impacted by a chemical, it is necessary to consider both prenatal and postnatal exposures in order to protect infants and children. Effects that occur in early development can dramatically impact children's well-being, quality of life, and survival (Wilson, 1977; Schardein, 1993, Kimmel, 2001). Birth defects are a major cause of infant morbidity and mortality in the U.S. Thus, potential for developmental toxicity from both prenatal and postnatal exposures is considered in the prioritization of the TACs for listing under SB 25. In considering developmental toxicants that are TACs, we determined whether developmental toxicity was the most sensitive endpoint for that compound. If other toxicological endpoints are observed at exposures lower than those necessary to induce developmental toxicity, then the developmental toxicity of the compound was not necessarily a driving force in prioritizing for further evaluation. Since RELs are based on the most sensitive endpoint, the REL for chemicals for which developmental toxicity is the most sensitive endpoint would be based on developmental toxicity. Those chemicals that have other endpoints more sensitive than developmental toxicity would have RELs based on those other endpoints. We used this information to help determine whether there were potential differential effects between infants and children and adults. Thus in considering the overall toxicity and potency of a compound, its propensity to induce developmental toxicity may not be enough to warrant listing under SB 25.

It is the legal opinion of the Office of Environmental Health Hazard Assessment (OEHHA) and the Air Resources Board (ARB) that Toxic Air Contaminants (TACs) that cause developmental or other adverse outcomes for infants or children as a result of prenatal exposure to those TACs are within the scope of SB 25. This legal opinion is based on a comprehensive reading of the

statutory language in SB 25, as well as the spirit and purpose of SB 25, and the legislative history of this piece of legislation. In addition, the conclusion that prenatal exposures that lead to developmental or other problems for infants and children is within the purview of SB 25 is consistent with good scientific and public health principles. The statute and accompanying legislative analyses are replete with references to protecting infants and children from the effects or impacts of air pollution. Accordingly, the point in time or means of exposure to a TAC is not determinative of whether or not something is within the reach of SB 25. Rather, the determining factor is whether an air pollutant differently affects infants or children as opposed to adults. If so, it is properly subject to SB 25. It should be noted tha. this opinion (that prenatal exposure leading to adverse outcomes in infants in children is within the scope of SB 25) is not based on an assumption or determination that a fetus is a child. Rather, as discussed above, it is based on the fact that exposures of the fetus to certain pollutants prior to birth may lead to adverse results that manifest themselves in infancy or childhood and that such exposures occurring in adulthood would not lead to similar toxicity.

2. Central Nervous System

Critical stages in the development of the central nervous system occur during embryogenesis and development of the fetus and postnatally through adolescence. Damage to the central nervous system is often irreversible because adult central nervous system neurons do not regrow after damage (Horner and Gage, 2000). Two key developmental processes in brain development are: 1) increase in brain mass (Dobbing and Sands, 1979) through proliferation of neurons and support cells, and 2) reinforcement of selected neuronal pathways through synaptogenesis.

The developing organism with rapid cell proliferation, migration, and differentiation is uniquely sensitive to disruption. In the brain these processes are unidirectional and occur at very specific times for different structures. Prenatal events include closure of the neural tube, proliferation of neurons and migration of cortical neurons. During infancy and early childhood, proliferation and migration continue along with synaptogenesis, myelination, and development of the blood-brain barrier. Structural maturation of neural pathways, including an increase in the diameter and

myelination of axons, continues through adolescence. During adolescence the rate of synaptic pruning peaks. Chemical exposures can have profound effects on all of these neurologic developmental processes (Rodier, 1994, 1995; Paus et al., 1999; Golub, 2000).

The brain increases in mass during the last month of gestation, and grows from 350 to about 800 grams during the first year of life (Boyd, 1962). Much of this increase is due to increases in the number of neurons and support cells in the brain. Exposures to xenobiotics such as lead or alcohol can interfere with increase in brain mass. Fetal alcohol syndrome is a recognized consequence of maternal-fetal exposure during the critical period of brain development (Clarren and Smith, 1978).

New neurons are produced from stem cells and progenitor cells that appear in the central nervous system very early in development (Jacobs et al., 2000). It was long thought that cell proliferation in the central nervous system ended early in life because stem cells ceased to be present. Recent research is finding that stem cells are present in the adult brain, and that cell proliferation continues into adulthood. Indeed, continued cell proliferation may be essential to maintain the health of the brain (Jacobs et al., 2000). In studies of adult nervous systems, it has been shown that stress as well as xenobiotic chemicals such as some psychoactive drugs can interfere with the proliferation of brain cells in the hippocampus (Jacobs et al., 2000). Since there is more cell proliferation in younger brains, they may be even more sensitive to the effects of stress and xenobiotics.

Another process that is critical for brain development is the selection of certain synaptic connections and the elimination of others. Neurotransmitters, such as GABA and acetylcholine, are essential to this process. Chemicals that interfere with the function of neurotransmitters can interfere with the development of synaptic connections. Such chemicals can also trigger apoptosis which results in the elimination of some neurons (Olney et al., 2000). Autism, an impairment of social interaction along with abnormal speech development and unusual behaviors, is associated with exposure to thalidomide. In humans, thalidomide exposure is linked to a 30 percent incidence of autism when exposure occurs on days 20 to 24 of gestation, but not before or after this time. This period corresponds with the production of the first neurons forming the motor nuclei of the cranial nerves; there is evidence of injury to these forming

nerves from thalidomide exposure (Rodier et al. 1997). This represents a clear example of how very specific critical periods exist during which irreversible events program future development. The effect of a chemical is dependent on the cellular process that it affects and the structures that may be undergoing that process at the time of exposure. Chemicals may affect multiple processes and multiple chemicals may affect the same process (see Table 6). Ethanol affects migration, differentiation, synaptogenesis and myelination and is capable of causing massive apoptosis during the period of synaptogenesis/brain growth of the third trimester. Ethanol interferes with multiple neurodevelopmental processes and causes Fetal Alcohol Syndrome in the fetus but is relatively nontoxic or even neuroprotective in the adult brain (Rice and Barone. 2000; Olney et al., 2000).

Arsenic administered orally to Wistar rats decreases acetylcholinesterase activity in the hypothalamus, cerebellum and brainstem, and slows the ability to learn and unlearn tasks. The effects are more pronounced in younger rats (Nagaraja and Desiraju, 1994). The authors concluded that the developing brain appears to be more susceptible to the neurobehavioral effects of arsenic than the adult brain.

Table 2. Chemicals associated with disruption of neurodevelopmental processes. Based on Rice and Barone, 2000 and Olney, 2000, Environ. Health Perspect.

Process	**Chemicals associated with disruption of this process in animals or humans**
Proliferation	Ionizing radiation, methylazoxymethanol (MAM), ethanol, methyl mercury, chlopyrifos
Migration	MAM, x-ray radiation, methyl mercury, ethanol
Differentiation	Ethanol, nicotine, methyl mercury, lead
Synaptogenesis	X-ray radiation, ethanol, lead, triethyltin, parathion, polychlorinated biphenyls (PCBs)
Gliogenesis and Myelination	Alterations in thyroid hormone homeostasis, ethanol, lead
Apoptosis	Ethanol, lead, methyl mercury, barbiturates, glutamine, halothane, ketamine
Neurotrophic Signaling	Aluminum, ethanol, cholinesterase inhibitors, methyl mercury

3. Endocrine System

The endocrine system consists of glands and other structures that secrete hormones directly into the circulatory system that in turn influence other bodily functions including growth and metabolism. Organs with endocrine functions include the pituitary, thyroid, parathyroid, adrenal glands, pineal body, the gonads, and pancreas. The endocrine system works together to coordinate and control development of the organism. Like the CNS, the endocrine system is extremely complex and imperfectly understood. The endocrine system is critical during the first few years of life, and during puberty.

Recently there has been some concern that environmental chemicals may be influencing important endocrine functions during development including changes that occur during puberty as well as the onset of puberty. The evidence for adverse effects from exposure to endocrine-

disrupting chemicals is sufficient to prompt action by the U.S. EPA which has initiated a program to test environmental chemicals for endocrine disrupter effects (Kavlock et al. 1996).

Thyroid hormones are critical to brain development *in utero* and through at least the first two years of life. Certain polychlorinated biphenyls (PCBs) and dibenzo-p-dioxins (PCDD) have been shown to alter the thyroid function during critical periods of thyroid-hormone dependent brain development resulting in neurological impairment in animal models (Porterfield, 2000). Impaired cognitive development has been noted in humans exposed prenatally to high levels of PCB in cooking oil (Chen et al. 1992). Prenatal exposure of children to PCBs from contaminated fish has been associated with lower IQ scores and decreased short-term and long-term memory, and ability to focus (Jacobson and Jacobson, 1996). These effects may be due to thyroid hormone disruption.

Sex hormone disruption that impacts children can also be caused by environmental toxicants. Rogan and others found an inverse relationship between DDE levels in milk fat and duration of lactation in women in North Carolina, possibly due to estrogenic properties of DDE (Rogan, et al., 1987). These results were confirmed in a study in Mexico where exposures to DDT were higher than in North Carolina (Gladen and Rogan, 1995). The same investigators found that boys with high pre-natal DDE exposure were heavier than other boys, and that girls with higher pre-natal PCB exposures were fatter than other girls (Gladen, Ragan and Rogan, 2000). These studies suggest that these xenobiotics act upon endocrine receptors and affect development.

4. Immune System

One of the major functions of the immune system is to protect the organism against infection. The development of the immune system results from a series of carefully timed and coordinated events during embryonic, fetal, and early postnatal life. Chemicals that excite or suppress the immune system during these critical periods can have a lasting effect on the ability of the system to respond to environmental challenges. There is evidence for a number of immunotoxic chemicals that exposure of pregnant animals at doses causing only transient effects in adults produces long lasting or permanent immune deficits in their offspring.

During fetal life, some cells of the immune system (the future T cells) develop first in the liver and then migrate to the thymus. They mature in the thymus and are released into circulation. Other immune system cells develop in the bone marrow. There are critical stages of development prenatally and during the early postnatal period. During these critical stages, the future immune system cells are increasing in number and becoming specialized in function. Endogenous chemicals present in the microenvironment where the future T cells develop regulate these processes. Xenobiotic chemicals that are capable of crossing the placenta, such as chlordane, benzo(a)pyrene, diethylstilbestrol or dioxin, have been shown to impede this development experimentally in rodents, resulting in some cases in early thymic involution and lifelong immunosuppression (Holladay and Smialowicz, 2000; Lai et al., 2000). Immunotoxic chemicals may also alter the ratio between different types of T cells or increase the incidence of autoimmune disease later in life (Holladay and Smialowicz, 2000). The implication is that immunotoxic chemicals that cross the placenta have the potential to permanently affect the development of the immune system in exposed fetuses or in newborns (Holladay and Smialowicz, 2000).

Chemical and physical agents that have been found to cause developmental immunotoxicity in rodents include (Holladay and Smialowicz, 2000):

- Polycyclic halogenated hydrocarbons: TCDD, PCB, PBB.
- Polycyclic aromatic hydrocarbons.
- Pesticides: hexachlorocyclohexane, chlordane, diazinon, DDT, carbofuran and hexachlorobenzene.
- Metals: methyl mercury, lead, and cadmium.
- Hormonal substances: estrogens and diethylstilbestrol, testosterone and cortisone.
- Therapeutic agents: acyclovir, busulfan.
- Mycotoxin: T-2 toxin.
- X-rays.

5. Respiratory System

5a. Lung Development

The lungs must be functional from the moment of birth, i.e. they must be able to absorb enough oxygen from the air and deliver it to the bloodstream to support the energy requirements of the developing child. Even though the respiratory system is functional at birth, it has only a fraction of the potential that it will develop during the early years of life. Chemicals that are toxic to the cells that line the alveoli can result in the development of lungs that have reduced alveolar volume and surface area. This will result in an adult with reduced lung capacity. Childhood exposure to such air pollutants as ozone, sulfur dioxide, particulate matter, and nitrogen dioxide is associated with decreased lung function, increased occurrence of respiratory illnesses, and exacerbation of asthma (Bates, 1995).

As discussed in the criteria air pollutant document developed under SB 25, the limited experimental and epidemiological studies currently available identify the early post neonatal period of lung development as a time of high susceptibility for lung damage created by exposure to environmental toxicants (Plopper and Fanucchi, 2000). For example, due to the relatively diminished defenses of their developing immune systems, infants are disproportionately susceptible to infections and other diseases. Indeed, in 1998 in the U.S., the rate (per 1000) of meningococcal disease by age group was 11.47 for <1 year versus: 2.75 for 1-4 years; 0.90 for 5-14 years; 1.27 for 15-24 years; 0.41 for 25-39 years; 0.49 for 40-64 years; and, 1.13 for >=65 years (CDC, 1999). Recent research indicates that there is a relationship between respiratory infections and air pollution effects in children (Sarafino et al., 1998). Thus, the higher rate of infectious diseases among infants is an indicator of diminished defenses against health insults, and is likely to cause them to have diminished reserves, and therefore to be more greatly affected by exposures to air pollution. Indeed, exposure to environmental tobacco smoke, an important source of indoor air pollution, is associated with increased infectious illness in children, such as middle ear infection (RR ≈ 1.62), and lower respiratory disease in young children (RR ≈ 1.5 to 2) (NCI, 1999).

In addition to their insufficiently developed immune systems, infants are growing rapidly, and limited recent evidence supports the hypothesis that environmental pollution can significantly alter development of the respiratory system at that period of life. In experimental animals, for

example, elevated neonatal susceptibility to lung-targeted toxicants has been reported at doses "well below the no-effects level for adults" (Plopper and Fanucchi, 2000; Fanucchi and Plopper, 1997). In addition, acute injury to the lung during early postnatal development causes a failure of normal repair processes, including down-regulation of cellular proliferation at sites of injury in animals. (Smiley-Jewel, et al., 2000, Fanucchi et al., 2000). Thus, it may be that both infants' diminished defenses and pollution-induced impairment of repair mechanisms can coincide during infancy, making the neonatal and post-neonatal period one of especially elevated susceptibility to damage by environmental toxicants.

The development of the respiratory system is closely linked with the development of the immune system. The airways and lungs are one of the main points of contact where pathogens can enter the body. Unlike the GI tract, the airways and lungs are not protected by strong acid. The immune system is therefore very active in patrolling the airways and lungs for foreign antigens. Chemicals that evoke immune responses in the airways can interfere with the development of both the respiratory system and the immune system. Exposure to environmental tobacco smoke in the home is also associated with asthma induction (RR of 1.75 to 2.25) in children as well as asthma exacerbation (RR of 1.6 to 2) in children (NCI, 1999). These effects may be due to interactions between effects on the immune system and respiratory system in children.

5.b. Asthma and Children

We have included exacerbation of asthma as a toxicological endpoint of particular concern to children. Asthma surveillance data developed by the national Centers for Disease Control and Prevention (CDC) (Mannino et al., 1998) and reports on asthma hospitalization by the California Department of Health Services (CDHS, 2000) both indicate that children, especially young children, are impacted by asthma morbidity more than older children and adults. The prevalence rates statistics indicate that a significantly higher percentage of children have asthma than adults (Mannino et al., 1998). The Centers for Disease Control report asthma prevalence rates per 1000 persons from their National Health Interview Survey by age group of 57.8 for 0–4 year olds, 74.4 for 5-14 yr olds, 51.8 for 15-34 yr olds, 44.4 for 35-64 yr olds and 44.6 for over 65 yrs. In addition, children have a smaller airway than adults have. Since the resistance to airflow is proportional to the fourth power of the radius, bronchoconstriction and increased mucin secretion

characteristic of asthma greatly increase airflow resistance in a small child relative to an adult. Thus, breathing difficulty is very significant in young children experiencing an asthma attack. Hospitalization rates for children 0 to 4 years are greater than all other age groupings (see Table 3), and is four-fold higher for black children than for white children (CDHS, 2000). Hospitalization, a nondiscretionary event, occurs only in severe cases. While hospitalization rate data are influenced by a number of factors including access to health care, we believe this information supports the concern that asthma impacts children more than adults. Therefore, TACs that exacerbate or induce asthma should be considered for listing under the Children's Environmental Health Protection Act.

Table 3 Doctor's Office visits, Emergency Room (ER) visits, and hospitalization for asthma by age

Age	Office per 1000	ER per 1000	Hospital per 10,000
0-4 yrs	50.3	120.7	49.7
5-14 yrs	51.5	81.3	18.0
15-34 yrs	22.8	69.2	10.0
35-64 yrs	41.7	64.4	15.2
> 65 yrs	44	29.5	25.5

Data from CDHS, 2000

6. Children's Cancer Risk

Risks of cancer from exposures to carcinogens occurring from conception through puberty can be different than those from exposures occurring in adulthood. There has been a steady, moderate increase in the incidence of childhood cancers (ages 0 to 20) since the 1970s, which has not been fully explained by improved diagnostics (Reis et al., 1999). Each year approximately 150 out of every million children (< 20 years of age) will be diagnosed with cancer. Leukemias, lymphomas and brain tumors are the most common cancers among children; germ cell and testicular tumors are also significant among adolescent age children (Perkins et al., 1997; Reis et al., 1999). Trends among these most common forms of childhood cancers over the past 20 years are as follows:

- The incidence of leukemia among children younger than 15 years of age increased by about one percent per year, driven primarily by increases in acute lymphocytic leukemia (Reis et al., 1999). It should be noted that Linet et al. (1999) evaluated the data on childhood

leukemia and report that the increased leukemia rates are dominated largely by a large increase in the early 1980s and appear to have leveled off since then.

- Incidence of Hodgkin's lymphoma has been declining by about one to two percent per year, while the incidence of non-Hodgkin's lymphoma has remained constant among children less than 15 years of age, but has increased from 11 to 16 per million among 15 to 19 year olds (Reis et al., 1999).
- Incidences of central nervous system cancers among children less than 15 years of age appear to have increased in a step-wise manner ("jumped") from a steady rate during 1973-1984 to a higher, but steady rate from 1985-1995. This change has been the subject of debate as to whether it is due to some environmental factor or due to improved diagnostics (Reis et al., 1999).
- Germ cell, trophoblastic and other gonadal cancers have steadily increased over the past 20 years among males and females 14 to 19 years of the age. The reason for the increase among adolescent boys is largely unknown. The increase among adolescent girls can be attributed in large part to inclusion of borderline ovarian cancers, which were not reportable cancers in earlier years (Reis et al., 1999).

Exposures to carcinogens during fetal development and in early childhood have been suggested as possible causal factors responsible for some of the increases in leukemia, lymphoma, brain and testicular cancers (Reis et al., 1999).

Exposure to a carcinogen early in life may result in a greater lifetime risk of cancer for several reasons. Cancer is a multistage process and the occurrence of the first stages in childhood increases the chance that the entire process will be completed, and a cancer produced, within an individual's lifetime. Tissues undergoing rapid growth and development may be especially vulnerable to carcinogenic agents. During periods of increased cell proliferation there is rapid turnover of DNA, and more opportunity for misrepair of damage (e.g., DNA breaks, crosslinks, adducts) or alterations (e.g., altered DNA methylation) to result in permanent changes to the DNA (e.g., mutations) that may ultimately lead to cancer. During early development, a greater proportion of the body's cells are relatively undifferentiated stem cells, and as such represent a large target population of somatic cells capable of passing along permanent changes to the DNA during future cell divisions. During development a larger percentage of the DNA is transcriptionally active and thus structurally more exposed and vulnerable to damage or

alteration by DNA reactive agents. There may be greater sensitivity to hormonal carcinogens early in life since the development of many organ systems is under hormonal control (e.g., male and female reproductive systems, thyroid control of CNS development). Other factors that may play a role in increased cancer risk from exposures during critical developmental periods include differences in immunological activity, intestinal absorption, biliary and kidney excretion, blood and fat distribution, and expression of enzyme systems that activate or detoxify carcinogens.

Evidence in humans of increased cancer risk following *in utero* exposure is provided by increases in the incidence of clear cell adenocarcinoma of the vagina in young women exposed to diethylstilbestrol *in utero* (DES daughters), in the absence of increased risk for this cancer in DES mothers (exposed as adults) (Preston-Martin, 1989). Human evidence of increased cancer risk resulting from exposures at critical periods during childhood is provided by observations of higher rates of radiation-induced breast cancer among women exposed during puberty, compared with those exposed after puberty (NRC, 1990b), and by observations of higher rates of leukemia and thyroid cancer among individuals exposed to radiation as children, compared with those exposed as adults (NRC, 1990b).

There is evidence in the epidemiological literature indicating that exposure to tobacco smoke during puberty may increase risk of breast cancer later in life, particularly among those that are NAT2 slow deacetylators (Marcus et al., 2000; Morabia et al., 2000; Lash and Aschengrau, 1999). Evidence in experimental animals of increased cancer risk following early in life exposure to carcinogens exists for a number of compounds, including urethane, vinyl chloride, DES, tamoxifen, nitrosourea compounds (e.g., methylnitrosourea), and alkenylbenzene compounds (e.g., safrole and estragole).

Numerous studies in rodents have demonstrated an increased susceptibility of the fetus, neonates and very young animals to urethane-induced cancers (Salmon and Zeise, 1991). Kaye and Trainin (1966) compared the incidence of lung tumors in mice exposed to urethane as newborns to that in mice exposed to urethane at 11-12 weeks of age, and found markedly increased tumor incidence and multiplicity in newborn mice as compared to older mice. Lung tumor incidence in newborns receiving single doses of 50, 100 and 180 mg urethane/kg body weight was 27%, 98% and 100%, respectively, ten weeks post-exposure, while tumor incidence in 11-12 week old mice

receiving larger single doses (100, 250, 500, and 1000 mg urethane/kg body weight) was 1%, 0%, 75%, and 100%, respectively. In another study, Rogers (1951) compared the tumorigenic effect of a single intraperitoneal injection of urethane in mice dosed at either two, four, six, eight or ten weeks of age, and found that lung tumor incidence and multiplicity decreased significantly as the age at exposure increased (e.g., from 100% tumor incidence and an average number of tumors per animal of 6.1 in mice exposed at two weeks of age to 76% tumor incidence and an average number of tumors per animal of 2.8 in mice exposed at ten weeks of age). The basis for this increased susceptibility is thought to be due to the fact that levels of esterases responsible for the detoxification and elimination of urethane are relatively low in newborns. This results in higher blood levels of urethane for longer periods of time, and provides greater opportunity for minor routes of urethane metabolism to occur, metabolically transforming urethane to the ultimate active carcinogen.

Vinyl chloride is another carcinogen for which the effect of age at exposure on tumor outcome has been extensively studied (Maltoni et al., 1981; Drew et al., 1983). In studies comparing the tumorigenic effects of vinyl chloride in rats exposed as either newborns or 11-week old animals, a significant tumorigenic response was observed in the newborn group (liver angiosarcoma and hepatocellular carcinoma), as compared with no increased incidence of these tumors in the 11-week old group (Maltoni et al., 1981). When rats, mice, and hamsters were exposed to vinyl chloride for 6- or 12-month periods starting at two, eight, or 14 months of age, the younger the age at first exposure, the greater the lifetime tumor incidence (Drew et al., 1983). Vinyl chloride has also been shown to induce higher levels of DNA adducts in livers of young animals (e.g., rats exposed at 11 days of age or 10-15 days of age), as compared with adults (Laib et al., 1989; Swenberg et al., 1992). Age-dependent differences in metabolism, leading to increased formation of DNA-reactive metabolites and increased DNA alkylation, combined with differences in cell proliferation rates, are thought to account for the increased susceptibility of young animals to vinyl chloride carcinogenesis. Researchers from the U.S. EPA have suggested a risk assessment framework for vinyl chloride exposure in which exposures to children are given greater weight (i.e., risk) compared to exposures later in life (Cogliano et al., 1996).

DES is a well-characterized transplacental carcinogen in animals, as well as humans (Newbold et al., 1998; Preston-Martin, 1989). DES induces rare uterine adenocarcinomas in mice exposed to

DES either prenatally or neonatally, and this carcinogenic effect has been shown to be multigenerational, with the offspring of female mice exposed perinatally also developing uterine adenocarcinomas (Newbold et al., 1998). The induction of reproductive tract cancers following early-in-life exposure to DES is thought to be mediated by the compound's estrogenic properties. This is supported by recent studies demonstrating that neonatal exposure to DES of transgenic mice over-expressing the mouse estrogen receptor results in an earlier onset of uterine adenocarcinoma, as compared to wild-type mice (Couse et al., 1997).

Tamoxifen is another carcinogen with estrogenic (and antiestrogenic) effects that has been shown to cause cancers of the female reproductive tract of rats and mice when exposures occur earlier, rather than later in life. When tamoxifen was administered to newborn female mice for the first five days of life, incidences of rare uterine adenocarcinomas of up to 50 % were observed (Newbold et al., 1997). An increase in uterine and other tumors of the reproductive tract was also observed in female mice exposed to tamoxifen *in utero* on gestation days 12-18 (Diwan et al., 1997). While no increase in tumors of the reproductive tract was observed in standard long-term bioassays of rats with tamoxifen exposures starting at five to six weeks of age (IARC, 1996), neonatal exposure on days two through five of life resulted in the development of rare uterine adenocarcinomas and squamous cell carcinomas of the vagina and cervix (Carthew et al., 2000). While the carcinogenic mode of action of tamoxifen in young animals remains unknown, these findings, taken together with the studies of DES, suggest that the developing reproductive tract is particularly sensitive to hormonally active carcinogens. The information obtained from studies of DES, tamoxifen, and estrogen may have value in predicting risk from early life exposures to other estrogenic compounds, based on a common mode of action.

The therapeutic agent AZT, used for the treatment of AIDS and in pregnant women with HIV to prevent transfer of the virus to the fetus, is a transplacental carcinogen in mice and to induce genotoxicity transplacentally in mice and monkeys (Olivero et al., 1997; Diwan et al., 1999). There is, therefore, a concern that children exposed *in utero* to this agent may be at higher risk of cancer. A definitive answer awaits long-term studies in humans.

Brain cancer is one of the leading childhood cancers in the U.S. Only a few chemicals are known to cause brain tumors in animals following exposure *in utero*. One class of compounds,

alkylnitrosoureas, is the most potent in causing brain tumors following *in utero* exposure in rodents (Maekawa and Mitsumori, 1990). Alkylnitrosourea compounds also seem to be more carcinogenic to the central nervous system following exposure to the fetus compared to exposure of adults. For example, *in utero* exposures to ethylnitrosourea were observed to be more than 60 times more potent in causing brain tumors than exposures during adulthood (Ivankovic, 1979).

Numerous studies have demonstrated that exposure of pregnant animals to nitrosourea compounds results in increases in the incidences of brain and other central nervous system tumors among offspring. These compounds include N-methyl-N-nitrosourea, N,N'-dimethyl-N-nitrosourea, N-ethyl-N-nitrosourea, N,N-diethyl-N'-methyl-N'-nitrosourea, N-propyl-N-nitrosourea, N-butyl-N-nitrosourea, N-methyl-N'-phenylnitrosourea and N-phenylmethyl-N-nitrosourea (CancerChem, 2000). Alkylnitrosoureas (e.g., methylnitrosourea, butylnitrosourea) can be formed in the gastrointestinal tract following ingestion of nitrite and alkylureas, which are present in the diet (Mende et al., 1991). Nitrosourea compounds are direct acting alkylating agents (e.g., mutagens). The reason that the brain is a target tissue for nitrosourea compounds is likely due to a reduced capacity of the brain and nervous system tissue to repair O^6-alkylguanine adducts relative to other tissues (reviewed in Maekawa and Mitsumori, 1990). It is not known why the developing animal is more sensitive to the carcinogenic effects of alkylnitrosourea compounds on the central nervous system, but it likely is due to genotoxicity of the nitroso compounds coupled with the rapid cell division and growth of the nervous system in the fetus and during the first weeks after birth.

Alkenylbenzene compounds such as safrole, estragole and methyleugenol cause a higher incidence of hepatic and other tumors in rodents exposed as newborns compared with rodents exposed as adults (OEHHA, 1999). The reason for this finding has not been elucidated. Safrole is a known transplacental and translactational carcinogen in animals. For all three compounds, exposure of newborn rodents (one to four doses only) resulted in high incidences of liver tumors (OEHHA, 1999). Liver tumors also occurred in rodents following long-term exposure of adult animals. These three structurally similar compounds share a common carcinogenic mechanism of action in rodents (OEHHA, 1999). The alkene moieties of each of these compounds are metabolized by the liver to a 1'-hydroxy derivative and several epoxide compounds. The 1'-hydroxy derivative is further conjugated with sulfate to form a sulfuric acid ester compound that

readily binds to DNA. Metabolism of estragole, and presumably safrole and methyleugenol, through this pathway appears to be quantitatively consistent among humans and rodents (OEHHA, 1999). Safrole, estragole and methyleugenol are naturally occurring substances found in a variety of herbs and other plants consumed as foods. Estragole and methyleugenol are also widely added to foods and consumer products for their flavor and fragrant properties.

To summarize, data in humans and animals for a variety of carcinogens suggest that exposures to such carcinogens early in life may result in a greater lifetime risk of cancer compared to exposures later in life. For example, humans exposed to ionizing radiation early in life have greater lifetime risk of leukemia, breast cancer and lung cancer than humans exposed later in life. Data from animal studies provide additional examples of increased sensitivity to early life exposures. These effects span a wide range of target tissues, including the liver (vinyl chloride, safrole), brain (methylnitrosourea), reproductive tract (DES, tamoxifen), and lung (urethane). Generally accepted methods for the assessment of carcinogenic risk from early life exposures are not available, although several approaches have been applied in specific cases (NRC, 1990b; Kai et al., 1997). In the coming year, OEHHA will evaluate the utility of various methods, as it develops guidelines for assessment of cancer risk following exposure to fetuses, infants and children.

C. Proposed Listing and Development of Tiers

We have placed 17 TACs chosen based on our literature reviews into two tiers (Table 4). Tier 1 consists of the TACs we propose to list under Health and Safety Code Section 39669.5(a) as possibly causing infants and children to be especially susceptible to illness. Tier 2 chemicals were thought to be less important for this initial listing of up to five TACs than Tier 1 chemicals for a variety of reasons. Polycyclic aromatic hydrocarbons (PAHs) are in Tier 1 because of evidence of developmental toxicity and increased susceptibility to genotoxicity (including carcinogenicity) in young animals and humans. These effects can have irreversible consequences. Exposure to PAHs is widespread, as these ubiquitous chemicals are products of incomplete combustion. Lead is in Tier 1 because it is a developmental neurotoxin. The increased susceptibility of infants and children is well established and the neurological effects are extremely prolonged. In addition, lead is a carcinogen. Although airborne lead exposures

have dropped due to removal of lead from gasoline, airborne lead exposures still occur as a result of stationary source emissions and re-entrainment of soil contaminated with lead. In addition, deposition of airborne lead onto soil, vegetation, and other surfaces results in exposure via ingestion. Polychlorinated dibenzo-p-dioxins (dioxins) and dibenzofurans (furans) and dioxin-like polychlorinated biphenyls (PCBs) are in Tier 1 because of developmental toxicity, effects on the immune system, endocrine systems, and carcinogenicity. Infants and children appear to be more susceptible to these effects which may result in irreversible changes. Dioxins and furans are also relatively ubiquitous products of incomplete combustion. PCBs, while no longer manufactured, are in the environment as a result of earlier use in electrical equipment and are minor products of incomplete combustion. In the case of acrolein, indoor and outdoor exposures are believed to be high, although data on typical ambient air concentrations are few. Nonetheless, this compound exacerbates asthma and therefore was placed in Tier 1. And finally, diesel exhaust particulate is ubiquitous in urban environments, and exposures are widespread. There are many studies demonstrating that diesel exhaust particulate can enhance allergic responses, and induce new allergies to airborne allergens. This raises concern for enhancement of allergic airway disease including asthma, and for development of new asthma. Diesel exhaust particles contribute to ambient PM10. Ambient PM10 has been shown to exacerbate asthma and has been associated with low birth weight and decreased lung function in children. In addition, diesel exhaust particulate contains PAHs (and other mutagenic polycyclic organic matter). As noted above PAHs can induce developmental toxicity and there is evidence that the fetus is more sensitive to genotoxicity of PAHs than adults. Thus diesel exhaust particulate was placed in Tier 1.

Formaldehyde is in Tier 2 because of some evidence indicating children may be more susceptible to the adverse respiratory impacts induced by formaldehyde exposure. Also, formaldehyde is a suspected human carcinogen and exposure to carcinogens early in life may result in a greater risk. Exposure to formaldehyde is widespread from a number of sources both indoor and outdoor. However, the evidence for differential effects is relatively weak and so formaldehyde was placed in Tier 2.

Benzene is in Tier 2 because of the concern that it may be leukemogenic in children and because of widespread exposure. Leukemia is an important endpoint to consider in evaluating impacts on

infants and children, since it is the major form of childhood cancer. Some epidemiological studies suggest that parental exposure to benzene is associated with elevated leukemia risk in children, indicating that a heritable mutation occurs in germ cells. However, other studies did not find this effect. Nonetheless, additional work needs to be done to resolve the issue.

While there is evidence that these chemicals may disproportionately impact infants and children, many Tier 2 TACs fell into that tier primarily based on lower potential exposures or inadequate data on exposure. There are limited exposures to vinyl chloride although stationary source (e.g., landfills) exposures may be important. However, the increased susceptibility of infants and children to vinyl chloride carcinogenesis is strongly supported by animal studies. Ethyl and methyl ethylene glycol ethers are developmental toxicants and can have profound irreversible effects. However, exposures are dropping because of the recognition of the toxicity of the methyl and ethyl ethers and actions taken by industry to reduce the use of these compounds. Unfortunately, data on emissions of specific glycol ethers from stationary sources are incomplete. Mercury is a developmental neurotoxin, and the increased susceptibility of infants and children to mercury compounds is well established. There are a number of sources of airborne mercury including combustion of municipal and hospital waste, although measured concentrations in ambient air are very small. It is an important toxicant but is outweighed by those chemicals in Tier 1. Non-coplanar PCBs are important developmental neurotoxicants that may produce irreversible effects. However, airborne exposures appear to be small, and their importance may be outweighed by those chemicals in Tier 1. Exposures to PCBs may be decreasing over time since intentional manufacturing and use of PCBs has ceased in California. Carbon disulfide is a neurotoxicant and possibly associated with developmental toxicity in animal studies, but exposures are low in California. Arsenic has potential differential effects in children from the standpoint of carcinogenicity and also potential neurotoxicity, but airborne exposures are low. Chlorine can exacerbate asthma, but exposures are low except in the case of accidental releases. Thus there is some concern for chlorine but not enough to place it in Tier 1. Methyl bromide is a neurotoxicant but little evidence is available to characterize differential effects. In addition, exposures from stationary sources are generally low and not widespread. Thus, it was placed in Tier 2. Methylene chloride is metaboliozed to carbon monoxide, a substance which differentially impacts infants. The ambient concentrations are low and represent about 0.005 the chronic REL (which is based on formation of carboxyhemoglobin).

Concern still exists because stationary source emissions in California are very high. Nonetheless, methylene chloride was placed in Tier 2. Manganese is a substance that is neurotoxic and animal evidence indicates that neonatal animals are more susceptible to the toxic effects of manganese. Exposures in California are generally low, and so manganese was placed in Tier 2. However, if exposures were to increase, we should reconsider listing manganese, as the evidence for differential effects in infants and children is adequate.

Table 4. TACs that may disproportionately impact infants and children. Tier 1 to be listed under Health and Safety Code Section 39669.5.

Toxic Air Contaminant	Endpoints of Most Concern	Major Reasons Why Chosen
Proposed Tier 1 TACs		
Acrolein	Respiratory Irritant	Exacerbation of asthma; modeling predictions indicate concentrations in urban air above cREL
Diesel exhaust particulate	Developmental effects, genotoxicity and lung cancer, respiratory irritant	Major source of ambient PAHs, PM10; exacerbation of asthma by PM10; PAH developmental toxicity and genotoxicity a concern.
Dioxins and dioxin-like PCBs	Developmental toxicity, immunotoxicity, endocrine disruption; thyroid effects	Widespread exposure; endocrine disruption at low body burden; young animals more susceptible than older animals
Lead	Developmental neurotoxicity/CNS effects	Children the most susceptible subpopulation due to developmental neurotoxicity.
PAHs	Developmental effects, genotoxicity and lung cancer	Animal studies indicate teratogenicity, and fetotoxicity; human studies indicate greater genotoxicity following in utero exposures.
Proposed Tier 2 TACs		
Arsenic	Carcinogenicity; potential neurotoxicity	Evidence of increased susceptibility to carcinogenicity early in life; possible neurotoxicity
Benzene	Hematopoietic effects, carcinogen	Widespread exposure; studies indicating increased risk of childhood leukemia in children of benzene-exposed workers.
Carbon disulfide	Neurotoxic effects; possible developmental toxicity	Neurotoxicity a key toxicological endpoint for children; metabolism slow in neonate; lower lethal dose in neonatal mice..
Chlorine	Respiratory irritant	Exacerbation of asthma.
Formaldehyde	Respiratory irritant; carcinogen	Widespread exposure; cREL below urban levels and indoor levels; exacerbation of asthma; indication that children more susceptible to lung function impacts.
Glycol ethers (EE and ME but not BE)	Developmental effects including teratogenicity	Teratogenic effects; large emissions of glycol ethers from stationary sources.
Manganese	Neurotoxicity	Neurotoxicity a key endpoint for infants and children.
Mercury	Developmental neurotoxicity	Children most susceptible subpopulation due to developmental neurotoxicity.
Methyl Bromide	Neurotoxicity	Infants and children are susceptible subpopulations for neurotoxicity.
Methylene chloride	Metabolized to carbon monoxide	Carbon monoxide has higher affinity for fetal hemoglobin; high emissions from stationary sources.
Noncoplanar PCBs	Developmental effects including neurotoxicity; thyroid effects	Infants susceptible subpopulation for thyroid effects; infants and children for developmental neurotoxicity
Vinyl chloride	carcinogenicity	Animal studies indicate much higher potency when exposure occur *in utero* or perinatally than as mature animals.

The following sections provide an overview of differences between children and adults that influence response to toxicants. Appendix C contains summaries of the top 11 TACs based on the prioritization described above and the results of the focused literature reviews. These summaries also provide a brief justification for our determination that these TACs disproportionately impact infants and children. Public and peer review comments will be considered in finalizing the list of the top five TACs pursuant to Health and Safety Code Section 39669.5(a). As mentioned above, identification of references on children-related susceptibility is more difficult than the standard chemical-specific literature search. Thus, we would also be interested in additional relevant studies for these eleven TACs.

III. Factors Influencing Why Infants and Children Might be More Susceptible Than Adults

Very few scientific studies in the published literature have explored the toxic effects of environmental chemicals on children. It has been standard practice to base risk assessments on adults, using adult parameters and data obtained from occupational studies, or studies in mature laboratory animals. An exception to this is in risk assessments where the sensitive toxicological endpoint is developmental toxicity. In standard risk assessment practice, health-protective assumptions have been utilized to attempt to account for individual variability in humans, including children, in response to toxicants. Thus as noted in Section I, we have made crude assumptions in most assessments of risk because data are generally lacking to make refined calculations on the difference between infants and children and adults in response to toxicants. More effort is needed to refine these assumptions and to ensure their adequacy in protecting infants and children. Data limitations will always be a problem.

There are a number of reasons to suspect that risk assessments based on adults may underpredict the risks of exposure in infants and children. The potential impact of environmental chemicals on children's health may be affected by behavioral, physiological, and sociological factors that differ from those of adults. Children have more limited diets than adults and higher intakes per body weight of food, fluids and air. These factors change both exposure patterns and responses to toxicants. Differences between infants and children and adults may result in significant illness

or disabilities in children but not in a similarly exposed adult. Minamata disease, or methylmercury poisoning, is one example in which prenatally exposed children were profoundly neurologically damaged by an exposure that was insufficient to produce clinical symptoms in the mother (Rogan 1995).

Assessments that adequately describe risks from exposures to children present challenges due to the rapid growth, changes in fluid and protein content, organ function, metabolic rates and enzymatic function that characterize childhood. Premature infants, term newborns, children, and adolescents are each unique in these parameters.

There is limited scientific information that addresses age-specific differences in sensitivity to toxic effects. A developmental neurotoxicity testing protocol, published by the U.S. Environmental Protection Agency in 1991 and later revised (Makris et al., 1998), has not yet been used extensively to evaluate pesticides for registration or reregistration much less for chemicals that end up as toxic air contaminants. An analysis by the Office of Pesticide Programs revealed that only 9 developmental neurotoxicity studies using this protocol on pesticides had been submitted to the agency between 1991 and 1998 (Makris et al., 1998). Six of the 9 studies identified endpoints that suggested a qualitatively different response between young animals and adults, leading to a more conservative risk assessment. These findings could not have been predicted by testing in mature animals only (Makris, 2000).

The vast array of differences that may affect toxicologic response to xenobiotic chemicals among the fetus, newborn and infants, children, adolescents and adults has not been catalogued in full. In the following sections we give examples of such differences that influence exposure and disposition of toxicants, and a few words on pharmacodynamic differences. This latter concept is tied more to the concept that different targets of toxicity are present in infants and children than in adults. (See the previous section B which described some critical organ systems where development and maturation are relatively prolonged.) While these examples are in no way a complete listing, they provide a foundation for understanding the variety of information that must be considered in order to anticipate the possible toxicologic risks to the growing and developing human.

A. Differences in Exposures: Infants, Children and Adults

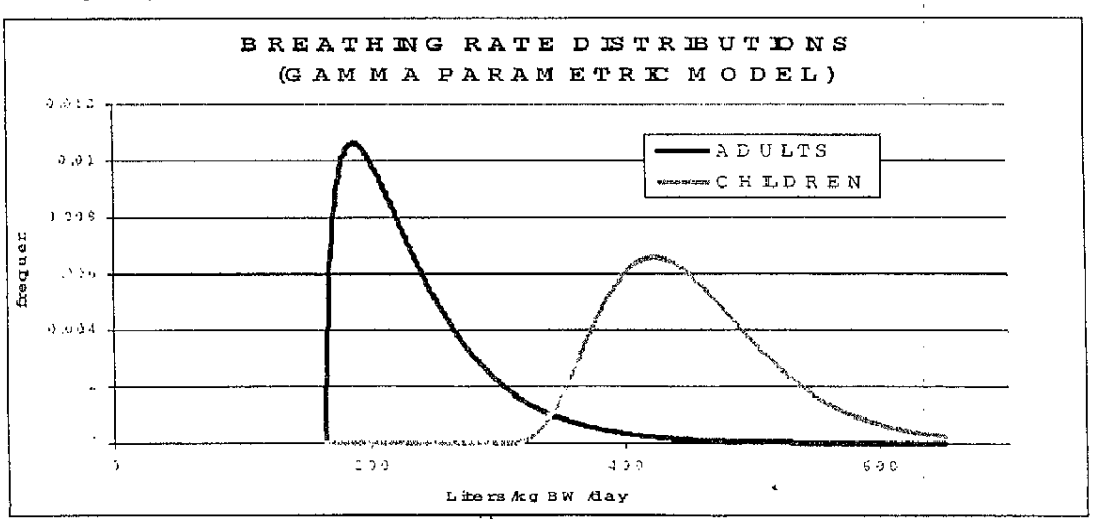
There is a growing body of evidence that children receive greater doses of environmental toxicants on a body weight basis than adults through common exposure pathways (such as inhalation and ingestion). These greater doses stem from greater exposures, from unique exposures, and from factors influencing the amounts of toxicants available at body sites where absorption occurs.

1. Inhalation Exposure

A primary physiological difference between children and adults is the higher breathing rates of children (Figure 1, below). This difference in breathing rates is due to the greater oxygen consumption rates of children, a result of their increased energy expenditure levels. Children expend more energy primarily because of their rapid growth and high levels of physical activity. Children also expend more energy for thermogenesis because they have a larger body surface area relative to their weight than adults.

Daily breathing rates are used to evaluate health risks from chronic exposure. Table 2 presents the mean and 95th percentiles of the distributions of estimated 24-hour breathing rates for children and adults illustrated in Figure 1 (OEHHA, 2000).

Figure 1. Frequency Distributions of Daily Breathing Rates for Children and Adults



* from OEHHA (2000)
children = 12 years of age or less
adults = greater than 12 years of age

Table 2. Daily Breathing Rates in units of L/kg-day

	Children (≤12 yrs)	*Adults (>12 yrs)*
Mean	452	232
High End	581	381

* from OEHHA (2000)

The mean breathing rate is almost twice as great for children as it is for adults (452 vs. 232 L/kg-day, respectively). Because children inhale a greater volume of air per unit time and body weight than adults do they receive higher doses of airborne contaminants.

There is also a difference in breathing rates between children and adults, which should be considered in estimating short-term exposures to toxicants. Adams (1993) measured short-term breathing (L/minute per body surface area) in the laboratory for different activities and activity levels (Table 3 and 4). The values presented in Tables 3 and 4 highlight the differences in short-term breathing rates between children of different ages and between children and adults.

Table 3. Mean (and Standard Deviation) of Minute Breathing Rates for Resting Protocols in units of L/min per body surface area

	3-5 years of age*	**6-12 years of age***	**13-59+ years of age** Female**	**13-59+ years of age** Male**
Lying	8.47 (1.96)	6.99 (2.67)	4.34 (0.84)	4.64 (0.83)
Sitting	8.89 (1.99)	6.75 (1.58)	4.70 (1.06)	4.84 (0.75)
Standing	9.25 (1.65)	7.79 (1.58)	5.08 (1.19)	5.53 (1.25)

*genders combined because there was no statistical difference between gender once normalized to body weight.
**age groups combined because there was no statistical difference between the age groups of 13-18, 19-59, and 60+ years of age

Table 4. Mean (and Standard Deviation) of Minute Breathing Rates for Walking Protocols in units of L/min per body surface area

	3-5 years of age*	6-12 years of age*	19-59 years of age Female	19-59 years of age Male
2.25 mph	15.79 (1.93)	NA	NA	NA
2.50 mph	NA	14.31 (1.92)	11.55 (1.30)	11.49 (1.72)

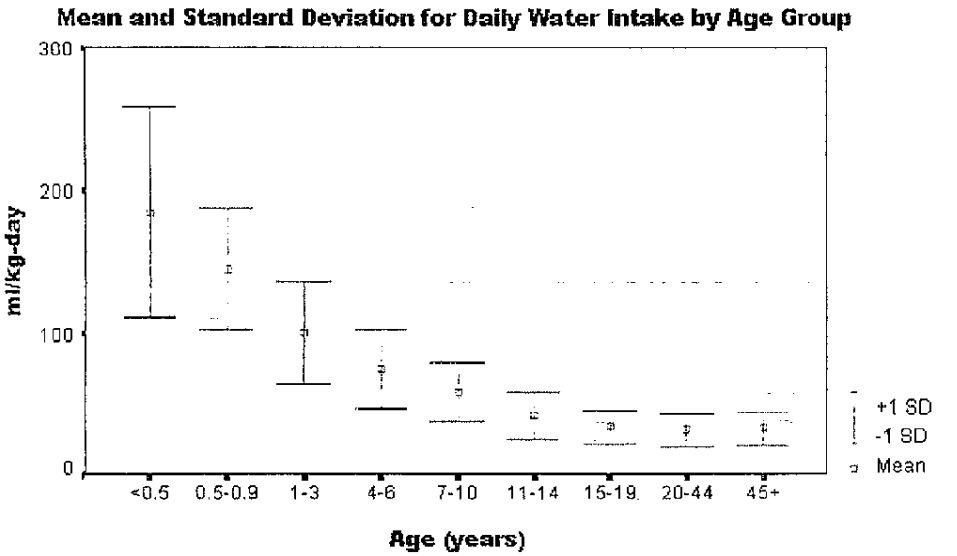
*genders combined because there was no statistical difference between the two groups
NA= not available

Another factor influencing inhalation exposure, in particular for particle exposures, is the difference in alveolar surface area between children and adults. Bronchioles develop completely prenatally but 85% of alveoli develop in the postnatal period. A newborn infant may have as few as 10 million alveoli while adults have up to 300 million (Plopper and Thurlbeck, 1994). This represents a greater than 20-fold increase in alveolar surface area. For particles, when viewed as a dose (number of impacted particles) per alveolar surface area, the disparities between the adult and infant/young child are even greater than on a body weight basis. The number of alveoli reaches about 90% of adult values by age three. At this point, the alveoli are smaller than in the adult. Alveolar surface area appears to be linearly related to body weight (Hislop et al., 1986). Alveolar surface area per unit body weight is thus approximately the same for the child as for the adult.

2. Water Intake Exposure Pathway

Children and adults have significantly different fluid intake requirements. Total fluid intake is estimated at 189 ml/kg-day for an infant 0-6 months of age while that of an adult is 35 ml/kg-day (Ershow and Cantor, 1989). Water consumption rates decrease with age and reach adult values in teenagers (Figure 2).

Figure 2.



* data from Ershow and Cantor (1989)

* total water intake (includes tap, bottled, other sources)

Infants have greater water requirements than older children. Infants may receive formula as their sole source of calories or in combination with breast milk for the first few months of life. Formula may continue to be fed after solid foods are introduced into the diet, often up to 12 months of age. Water from various sources (tap, bottled, well) is used to prepare formula and may contain toxicants, such as metals, and chlorinated organic compounds. Because formula may be the infant's sole source of fluids and nutrients for at least the first few months of life, and because infants consume greater quantities of fluids on a body weight basis than adults, formula-fed infants may receive greater doses (on a mg/kg body weight basis) of water-borne contaminants than older children and adults.

3. Breast Milk Exposure

Breast milk intake is an exposure route unique to infants. It represents an additional source of toxicant exposure that older children and adults do not have. An infant's sole source of nutrients is typically breast milk or formula, for at least the first few months of life. A breastfed infant would thus receive repeated doses of any contaminants present in the breast milk.

A number of factors influence the movement of chemicals from the mother's plasma into breast milk, including the lipophilicity of the compound which determines ability to partition into milk fat, protein binding in plasma and milk, and influence of pH of milk and plasma on ionization (Findlay, 1983; Fleishaker et al., 1987). The pH of breast milk (6.6-6.8) is more acidic than plasma. Therefore basic compounds can attain higher concentrations in breast milk than plasma as they become trapped by ionizing at the more acidic pH of the milk (Findlay, 1983). A chemical that is highly protein bound in the plasma may not be available for transport into milk. However, if the chemical has higher affinity for milk protein than plasma protein, then it may be pulled into the milk preferentially (Findlay, 1983). These factors may all apply, and predictions of concentrations of a drug or environmental chemical in breast milk are difficult (Wilson et al., 1985).

Chronic exposure to highly lipophilic, poorly metabolized environmental contaminants results in the concentration of these contaminants in adipose tissue and breast milk lipid. The contaminant levels in breast milk lipid appear to be in equilibrium with those in adipose tissue. These contaminants are eliminated from body adipose stores extremely slowly and through breast milk during lactation. Over time the breast-fed infant may receive a significant portion of the total maternal contaminant load (Smith et al., 1987; Schecter et al., 1996). For a toxicant such as tetrachlorodibenzo-p-dioxin (dioxin), an infant's intake rate (pg/kg-day) from breast milk may be substantially greater than the mother's environmental intake rate (pg/kg-day) (Hoover et al., 1991). Based on measurements of dioxins and PCBs in the diet and in breast milk, the Toxic Equivalent (TEQ) intake of dioxin and PCBs on a picogram/kg-body-weight basis is about 50 times greater for the breastfeeding infant than for the adult (Patandin et al., 1999).

Breast-feeding infants may also be exposed to non-lipophilic contaminants in breast milk. For example, 36-80% of lead blood levels in a breastfeeding infant during the first 60-90 days postpartum may be attributed to lead in breast milk (Gulson et al., 1998). Hallen et al. (1996) demonstrated in rats that lactational transfer of lead is considerably higher than placental transfer in recently or currently exposed animals. Mercury concentrations in breast milk have been shown to correlate with presence of amalgam fillings (Oskarsson et al., 1996). There have been

a number of studies demonstrating the presence of drugs in breast milk. Codeine and morphine concentrations in breast milk were over twice those in the mother's plasma (Findlay, 1983), while caffeine and acetaminophen concentrations in the milk and plasma were equal. Salicylate, a weak acid, showed higher peak concentrations in plasma than in milk.

Because the prevalence of breastfeeding has increased significantly, this exposure pathway has become more important in the health assessment of population-wide exposures. In 1999, 67.2% of newborns were breast-fed, which is greater than at any time since the 1940's (Ross Products Division, Abbott Laboratories, 2000; Fomon, 1993). The prevalence of breastfeeding at 6 and 12 months of infant age, a reflection of the duration of breastfeeding, has increased proportionately. In 1999, 17% of all infants 12 months of age were still being breastfed (Ross Products Division, Abbott Laboratories, 2000). Thus, breast milk is a common route of potential exposure of infants to toxicants.

4. Food Intake Exposure

Children's caloric needs are greater than that of adults. The recommended dietary allowance (RDA) for a reference (median of the population) child 1-3 years of age is 102 kcal/kg-day, whereas that for an adult male (19 years or older performing light to moderate activity) is 40 kcal/kg-day and an adult female is 38 kcal/kg-day (NRC, 1990a). This results in greater food intake rates per unit body weight for children relative to adults and thus increased doses of contaminants in or on food.

During weaning, when solid foods are introduced into an infant's diet, the foods are often from the same food source (such as apples consumed in the form of both juice and applesauce) or the same food type (such as apples and peaches, both fruits). Thus weaning infants tend to consume more of one particular food source than adults or older children and may receive repeated doses of contaminants that may be in or on that food source. Although some infants may receive different types of fruits and vegetables, pesticides with a common mode of action that are used on one source of fruit or vegetable may also be used on other fruits and vegetables. Setting of allowable pesticide residue levels attempts to account for this.

Toddlers and young children also tend to consume diets with less variety than an adult's diet. Often this is due to a child's dietary preferences, with some children eating only a few food items for weeks at a time. This results in a dramatically increased consumption of particular food items by children compared with adults. For example, on average, non-nursing infants consume over 16 times the average U.S. consumption of apple juice (NRC, 1993). The greater intake of particular foods by children increases further the difference between child and adult doses to food-borne contaminants.

5. Soil Ingestion Exposure

People's activities largely determine their exposure to soil and dust (Wiley et al., 1991a,b; U.S. EPA, 1995; Kissel et al., 1996), but frequencies and durations of soil exposures are not well characterized. The U.S. EPA Exposure Factors Handbook (1995) used data from Hawley (1985) to estimate that children were in contact with soil 130 days per year compared to 45 days per year for adults.

There is general consensus that children ingest more soil than adults due to their frequency of contact with soil and with objects that have contacted soil (see the section *Location as a Factor Influencing Exposure*, below). Young children likely receive greater doses of contaminants through soil ingestion than older children because their mouthing behavior (see *Behavioral Factors Influencing Exposure*, below) is more frequent, and because differences in hygiene, crawling and other activities result in greater soil contact.

Pica is a behavioral anomaly characterized by the ingestion of nonfood items, including soil. The incidence of pica is not well characterized but is not considered uncommon. It is most prevalent in children three years of age and younger (Barltrop, 1966). The prevalence of soil pica in children is difficult to estimate because soil pica has been arbitrarily defined (the ingestion of more than one gram of soil per day) and because pica is an erratic behavior (pica children do not consistently eat greater than one gram of soil per day). Nonetheless, because soil pica is very rarely seen in adults, it represents an exposure route most applicable to children. Children may thus receive higher doses of contaminants deposited onto soil than adults do.

Children may also receive large single doses of contaminants due to soil pica. The doses may be sufficiently great to cause acute toxicity, including lethality (Calabrese et al., 1997).

6. Behavioral Factors Influencing Exposure

Children are more physically active than are adults. Their high energy expenditure requires these children to consume greater quantities of food, air, and water on a body weight basis than adults. This increases the dose of toxicants the children receive from inhalation, food and fluids. The studies of California children's and adult's activity patterns found appreciable differences in the amount of time spent per day by children and adults in physical activities (Wiley et al., 1991a,b). The mean time spent per day in active sports for children was 50 mins/day compared to 13 mins/day for adults. The mean time spent per day walking or hiking for children was 22 mins/day compared to 5 mins/day for adults. The increased physical activity can also result in increased soil contact (e.g., playing soccer).

Children are more highly exposed to contaminants from soil and dust than are adults. Infants and young children frequently play on the floor. When outdoors, toddlers and young children typically crawl, lie, sit, and play on the grass or soil. They explore their environment by touching and manipulating many different objects. Infants and toddlers frequently put hands, toys, and other objects in their mouths. This is a normal childhood behavior. Infants are born with a suckling reflex that aids in obtaining food and provides them with a sense of security and comfort, as in thumb sucking. Infants will also put hands and objects in their mouths when they are teething. Though children may only mouth body parts and objects for a few seconds, infants 6-12 months of age were observed to spend an average of 44 minutes per day in this activity (Groot et al., 1998). The body parts and objects that are mouthed often have toxicants on their surfaces because they tend to be in frequent contact with ground surfaces such as carpet or soil where pesticides may have been sprayed or where contaminants have settled. This mouthing behavior may lead to significant doses of pesticides and other contaminants (Zartarian et al., 2000) that adults do not receive.

Some older children may be more highly exposed to contaminants than younger children and adults due to their participation in sports and athletic activities. These activities often result in

greatly increased breathing rates, sometimes for relatively long periods of time (as in soccer, track, cycling, and swimming). This may result in increased inhalation doses of air pollutants relative to typically less active adults.

7. Children's Immediate Environment as a Factor Influencing Exposures

Children spend more time outdoors and in active play and sports than adults. A study of activity patterns in California found that children under 12 years of age spent an average of 124 minutes per day engaged in outdoor activities including sports compared with only 21 minutes for adults (Wiley et al. 1991a,b). This study also found that children spend approximately 70% of their time outdoors between 12:00 noon and 8:00 p.m., when outdoor pollutants tend to register at the highest levels in urban areas.

Newborns and young infants spend considerable time in a crib or other single environment as opposed to moving about as do older children and adults. An infant is likely to receive greater exposure to a substance in a single environment than an older child or adult who moves in and out of that environment. Infants and toddlers may be unable to move away from noxious stimulants and thus receive greater doses of the toxicant than an older child or adult. For example, an infant in a crib may receive greater doses of tetrachloroethylene, a carcinogen, from clothes that have been recently dry-cleaned, and that are in or near the infant's room, than would an adult in the same household. Infants and children are also exposed to environmental tobacco smoke (ETS) which is an important source of exposure to toxic air contaminants indoors such as polycyclic aromatic hydrocarbons, benzene, aldehydes including acrolein and formaldehyde, and metals such as lead and nickel. Summaries of the impacts of some of these compounds on infants and children are in Appendix B. ETS exposure has been causally associated with respiratory illnesses, including lung cancer, childhood asthma and lower respiratory tract infections (NCI, 1999). ETS exposure may be implicated in 120 SIDS deaths per year in California (RR ≈ 3.5), with a risk of death to 0.1% of infants exposed to ETS in their homes (NCI, 1999).

As noted above in Section 6, children have more frequent contact with ground surfaces than adults. They are shorter in stature and young children have less motor coordination and stumble

frequently. Thus children likely have greater exposure to contaminants deposited onto surfaces and especially the ground or floor than adults.

Vapors that are heavier than air in the indoor environment will be concentrated near the floor, the breathing zone of young children. While the breathing zone for an adult is four to six feet above the floor, the breathing zone for an infant may be a few inches above the floor (Bearer, 1995). In a tragic case in Michigan, a four-year old child became acutely intoxicated from mercury used in indoor paint. A factor thought to be important in this case was that mercury vapor tends to collect at floor level, near a child's breathing zone and where they tend to play. In addition, the breathing rate per unit of body weight is higher in preschoolers than in adults. These factors may have resulted in acute poisoning of the child, even though the adults in the household were not clinically affected (CDC 1990).

8. Dermal Exposure

Infants and children have a greater body surface area to body weight ratio than adults. This ratio is more than two times greater in a newborn infant than an adult (U.S. EPA, 1997). The infant's greater body surface area results in increased exposures, on a body weight basis, to dermal toxicants. This increased exposure is likely the primary reason that dermally applied pharmaceuticals are more toxic to infants (U.S. EPA, 1992).

Skin permeability can influence dermal absorption. The newborn infant may not have fully keratinized skin (Bearer, 1995) and therefore may have greater skin permeability than at any other age. The age at which keratinization is complete is uncertain, though there is suggestion that it may occur within days of birth. Thus increased skin permeability in the neonate may only last a few days. Child behavior can significantly impact skin permeability. For example, when the skin moisture content is increased above its normal level, skin permeability increases 2-3 fold (Klaassen, 1996). Because children often mouth their hands or other body parts wetting the skin, these mouthed sites may be more permeable to dermal toxicants. The U.S. EPA's Exposure Factors Handbook (1997) reports that hands, knees, and elbows have the highest soil adherence. Thus infants and children who frequently mouth and thus moisten their hands might receive doses of dermally absorbed toxicants that adults might not receive.

When skin is covered by clothing or by hair, the dose of toxicant absorbed is generally smaller. Infants often have very little hair for the first several months of life. This results in increased doses of toxicants that may be in pillows, blankets, clothing, and house dust relative to adults. Because children are more active than adults and because they may become overheated during play and periods of high activity, children may often have non-clothed areas of arms, legs and feet.

B. Differences in Disposition of Toxicants

1. Absorption

Characteristics of absorption of chemicals show age-related trends from birth through early childhood. A number of factors may result in significant differences in the absorption of environmental pollutants by infants and children versus adults. Ingestion is a major route by which infants and children are exposed to environmental chemicals (U.S. EPA, 2000). Most toxicants administered orally are absorbed into the circulatory system by passive diffusion through the lining of the stomach and intestines. The two factors most affecting this process are gastric pH and emptying time (Milsap and Jusko, 1994), both of which vary with age from birth through infancy and childhood. At birth the gastric acidity is weak or neutral (pH 4-8) due to the presence of amniotic fluid in the stomach (Avery et al., 1966). Following birth, gastric acid appears in the first several hours to two days of life, decreases for about 10 days, then increases approaching adult levels by three months of age (Miller, 1941). Premature infants may continue to have lower gastric acidity due to immature acid secretion (Agnoud et al., 1969). The pH of the stomach influences the absorbed dose of a chemical by altering its ionization state. This alters the potential dose to the infant of ionizable contaminants that are absorbed from the stomach.

The gastric emptying rate in neonatal infants is variable and prolonged (Siegner and Fridrich, 1975; Siegel et al., 1984) and is affected by both gestational and postnatal age. In 24 infants aged one to ten weeks gastric emptying of 50 milliliters of milk containing Indium-113m followed an exponential pattern with an average half life of 87±29 minutes. Absorption rates for several chemicals, such as phenobarbital, digoxin, arabinose, and xylose, increase throughout the

first year of life. While delayed absorption seen in neonates is partially due to slower gastric emptying and gastrointestinal motility, other factors such as lower pancreatic enzyme function and bile acid secretion as well as a less developed unstirred water layer on the intestinal mucosa also play a role (Murphy and Signer, 1974; Heimann, 1980). Bile salt secretion is reduced in newborns compared to adults and may result in decreased absorption of lipid-soluble chemicals (Besunder, 1988).

The lungs are the major point of entry of airborne environmental pollutants into the body. Children may absorb more chemical through the lung in any given setting than an adult because of their increased breathing rate per unit body weight (i.e., mL/kg/m^2/min) (Snodgrass, 1992).

Environmental chemicals, which are often lipophilic, may pose a greater risk to children due to the possibility of enhanced dermal uptake due to increased skin surface area and permeability. Dermal absorption may be significantly higher in neonates due to an immature epidermis and increased skin hydration. The surface area/bodyweight ratio is also much higher in infants and children than adults (0.067 to 0.033 m^2/kg vs. 0.025 m^2/kg in adults) (Snodgrass, 1992). Severe toxicity has been observed in infants following dermal application of hexachlorophene (Tyrala et al., 1977) and isopropanol (McFadden and Haddow, 1969). Dermal absorption as affected by age and related physiological differences has not been fully characterized.

To summarize, childhood differences affecting absorption of environmental chemicals include:

- Lower gastric acidity in neonates.
- Slower gastric emptying in neonates.
- Lowe intestinal absorption in neonates compared to children.
- Higher breathing rates in infants and children than adults.
- A higher surface area/body weight ratio (0.067 in newborn vs. 0.025 in adult).
- More permeable skin surface (in premature infants especially).

2. Distribution

The distribution of absorbed chemicals in the infant and child is affected by the concentration and types of plasma proteins and the relative size of fluid, fat and tissue compartments of the body (Milsap and Jusko, 1994). Total body water may be as high as 85 percent by weight in

premature infants and 78 percent in full-term neonates versus 50-60 percent in adults (Friis-Hansen, 1961, 1971). The portion of fluid that is extracellular decreases from gestation (65%) to puberty (20%) (Reed ,1996). The percentage of body water affects the volume of distribution of absorbed drugs and other chemicals. The apparent volume of distribution (Vd) relates the amount of chemical in the body to its plasma concentration. Chemicals that are more water-soluble have higher volumes of distribution and lower clearance rates in infants than in adults. Those that are more lipophilic would have lower volumes of distribution and increased blood concentrations and therefore relatively more rapid clearance in infants. For example gentamycin, theophylline and phenytoin show two to three-fold higher Vd's (L/kg body weight) in neonates versus adults. Conversely, diazepam, which is more lipophilic, had a volume of distribution in neonates only one-third that of adult values (Milsap and Jusko, 1994).

The binding of absorbed chemicals to plasma proteins is an important determinant of toxic response because bound toxicant is not available for action at the receptor. The extent of binding depends upon the quantity of binding proteins available, the binding or affinity constant of the chemical for the protein(s), the number of available binding sites, and the presence of pathophysiological conditions which may alter the binding interaction (Besunder et al., 1988). The affinity of plasma albumin for acidic drugs increases along with total plasma protein concentration from birth into early infancy (Morselli et al., 1980). The reduced plasma protein binding of drugs in newborns is probably due to reduced total plasma protein concentration as well as such qualitative differences as persistence of fetal albumin with lower affinity for drugs and lower levels of γ-globulins and lipoproteins (Morselli et al., 1980). Plasma albumin, total protein concentrations, and α_1-acid glycoprotein do not reach adult values until one year of age (Herngren et al., 1983; Brodersen et al., 1983). Three of the drugs noted above (theophylline, diazepam and phenytoin) exhibit lower protein binding (1/3 to 1/10, respectively) in neonates versus adults (Morselli, 1976; Morselli et al., 1980; Rane and Wilson, 1976). In addition to the quantitative and qualitative differences in plasma proteins during early development, disturbances in acid-base balance and increased blood concentrations of endogenous substances, such as free fatty acids and bilirubin, can affect protein binding of drugs or the release (i.e., displacement) of bound drugs or other exogenous chemicals (Brodersen et al., 1983). Trichloroacetic acid (TCA), a metabolite of perchloroethylene (PCE) and trichloroethylene

(TCE) is very highly bound to albumin (Muller et al., 1972). Lower levels of albumin may result in a larger volume of distribution and also higher unbound TCA in the blood. Additionally, bilirubin and free fatty acids, often present at elevated levels during the first weeks of life, competitively bind with albumin and may displace TCA leading to greater potential for acute toxicity (Ginsberg, 2000).

Relative brain mass and brain perfusion in infants and children are greater than in adults. A newborn's brain is one-third the size of an adult brain while its body weight is only about four percent of an adult's (i.e., 3.0 vs. 70 kg) (Snodgrass, 1992). A ten-year old child has a cerebral flow of about 50 L/kg-hr vs. 40 L/kg-hr in an adult (Roberts, 1984). The blood-brain barrier refers to the multiple anatomic and physiologic factors that prevent or slow the entry of toxicants and drugs into the central nervous system. This barrier is not fully developed at birth, which is why some chemicals are more toxic to newborns than to adults. Morphine is three to ten times more toxic to newborn than to adult rats due to the higher permeability of the brain in the newborn to morphine (Rozman and Klaassen 1996).

Childhood factors affecting distribution of xenobiotics include:

- Higher total body water/body weight.
- Lower body fat/body weight.
- Lower mass of skeletal muscle/body weight.
- Higher relative brain and liver weights vs. adult (6-fold and 2.5 fold, respectively).
- Lower concentrations of plasma proteins which can bind pollutant chemicals.
- Fetal hemoglobin present in neonates (nitrate/nitrite sensitivity).
- Blood pH is lower in neonates.
- Increased permeability of the blood-brain barrier in early life.

3. Metabolism

The ontogeny of metabolic pathway development during early life may result in important changes in rates of activation to toxic intermediates, detoxification, and clearance of xenobiotic compounds. Many of the hepatic microsomal enzyme systems responsible for drug metabolism are present at birth and their activities increase rapidly to near adult levels early in life (Morselli et al., 1980; Morselli, 1989; Dutton, 1978; Aranda et al., 1974). Liver phase I reactions

(oxidation, reduction, hydroxylation) develop rapidly during infancy, with adult levels attained by six months of age (Neims et al., 1976; Dutton, 1978; Aranda et al., 1974). The total cytochrome p450 content of human liver microsomes is unchanged from fetal life through the first year of post-natal life and is approximately one third the total adult content (Treluyer et al., 1991). The postulated development of individual cytochrome P450 (CYP) forms during infancy and childhood is summarized in Table 5. Except for CYP3A4 and CYP3A7 the table values are based on immunological analyses for the presence of CYP mRNA and protein rather than on the metabolism of specific chemical substrates. In general, three groups of P450 could be described: CYP3A7 and CYP4A1 present in fetal liver and active on endogenous substrates; an early neonatal group including CYP2D6 and 2E1 which surged within hours of birth; and a later developing neonatal group, CYP3A4, CYP2C's, and CYP1A2 (Cresteil, 1998). Treluyer observed that treatment of infants with barbiturates resulted in induction of CYP2C activity and increased metabolism of diazepam and tolbutamide (Treluyer et al., 1997).

Table 5. Postulated Developmental Expression of Individual P450 Forms in the Human Liver (adapted from Hakkola et al., 1998; Cresteil, 1998)

Form	Fetus (% of total P450)	Neonate <4 weeks	Infant <12 months	Child <15 years	Adult (% of total P450)	Substrate or Class Metabolized
CYP1A1	+	?	?	?	+	Aryl hydrocarbon hydroxylations, 2-acetylaminofluorene, phenoxazone ethers (Sonnier & Cresteil, 1998)
CYP1A2	-	+	+	+++	+++ (18)	Aromatic amines, caffeine *N*-3 demethylation (Sonnier & Cresteil, 1998)
CYP2A6	-	?	+	++	++ (6)	Coumarin 7-hydroxylation
CYP2A7	-	?	?	?	?	
CYP2B6/7	-	?	++	?	+ (<1)	Hexane, cyclophosphamide
CYP2C	+/?	++/+	++	+++	+++ (25)	Tolbutamide, diazepam, phenytoin, barbiturates-hydroxylation, demethylation (Treluyer et al.1997)
CYP2D6	+/±	++/+	+	+	+ (2)	NNK, debrisoquine, nortryptiline, sparteine, Dextromethorphan (Treluyer et al., 1991)
CYP2E1	±	±/+	+	++	++ (9)	Benzene, halogenated solvents, nitrosamines, styrene, acetaminophen, chlorzoxazone (Vieira et al., 1996)
CYP3A4	+/-	++	++	+++	+++ (40)	Benzo[a]pyrene-7.8 diol, aflatoxin, 1-nitropyrene; hydroxylation of dehydroepiandrosterone (Lacroix et al., 1997)
CYP3A5	+	+	+	++	++ (10-30)	
CYP3A7	+++ (30)	++	+	+	-	Hydroxylation of dehydroepiandroster-one (Lacroix et al., 1997)

Note: Symbols for detection of CYP mRNA/protein (when different): ? unknown, - not detected, ± possibly present in small quantities, + present in low concentration, ++ present in moderate concentration, +++ present in high concentration.

There has been some study of the development of human p450 enzymes in the liver but very little research about the timing of development of activity in other tissues. In one study, sex and age related differences in CYP1A1 activity in the human brain were documented. During childhood, enzyme activity increased dramatically and reached adult levels by puberty.. In the lung, animal studies have shown that exposure to environmental toxicants (side-stream tobacco smoke) can alter the developmental profile of cytochrome P450 enzymes inducing earlier activity (Gebremichael et al., 1995). Repair of injured pulmonary Clara cells by toxicants activated by cytochrome p450 enzymes is decreased in the early postnatal period in rabbits and neonatal injury alters bronchiolar organization in the adult (Smiley-Jewell et al., 2000; Smiley-Jewell et al., 1998). In general, the level of inducibility of fetal CYP forms is unknown (Hakkola et al., 1998).

Phase II conjugation reactions are generally reduced at birth (Milsap and Jusko, 1994). Conjugation with glucuronic acid is significantly lower at birth with activities 2.5-fold below adult levels (Levy et al., 1975). Glucuronidation generally matures to adult levels in two months although glucuronidation of some drugs does not reach adult levels until puberty (Snodgrass, 1992). Reduced glucuronidation would result in slower removal of aniline, *N*-hydroxyarylamines, phenol, and benzene metabolites in neonates. Acetylation and sulfation reactions are generally high in newborn infants and rapidly reach adult levels. Thus neonates may conjugate drugs or environmental chemicals with sulfate rather than glucuronic acid (e.g., acetaminophen). *N*-Acetylation reactions occur in neonates (e.g., β-naphthylamine). Glutathione (GSH) sulfotransferases (GSTs) occur in different forms. GST-P is prevalent in the fetus and decreases postnatally. GST-mu and GST-alpha are low at birth but develop during the first three to six months of life. GST-mu is involved in arene oxide detoxication. GST-alpha is two-fold more active in children 0.5-4 years of age than in adults. Plasma GSH is similar in children 0.5-4 years of age and in adults (Ginsberg et al., 2000). Blood esterase activity is more depressed in premature infants than in full-term infants and doesn't reach the latter's activity for 10-12 months. Esterase activity in newborns is one-tenth to one-half the adult level. Low esterase activity coupled with lower volume of distribution may account for the prolonged effect of local anesthetics observed during delivery (Ecobichon and Stevens, 1973).

As a result of differing enzyme activity, some chemicals are metabolized by wholly different metabolic pathways at different ages. In infants, theophylline is N-methylated to caffeine. In adults this is a minor pathway, the majority being N-demethylated or C-oxidated to monomethylxanthines or methyl-uric acid. A pattern of metabolism similar to adults is achieved by seven to nine months of age (Reed, 1996). Renwick compared age-related differences in the pharmacokinetics of 36 drugs which are eliminated by different processes (Renwick 1998; Renwick et al., 2000). His calculation of internal doses as the area under the blood concentration times time curve (AUC) for the same doses (mg/kg) indicated that the major difference from adults occurs in preterm and full-term infants and neonates. The authors also compared seven drugs which are substrates for glucuronidation, one with substrate specificity for CYP1A2, and four with substrate specificity for CYP3A4 metabolism. Each showed the relatively higher AUC internal doses in neonates and young infants versus adults. The interindividual variation in elimination by these three routes did not differ by age group. Renwick et al. (2000) concluded that the main factor affected by age is the overall difference in clearance and the internal dose in neonates and children compared with adults and not the extent of variability.

In the pediatric medical literature the phenomenon of drug-drug interactions is well documented. These interactions may occur by different pharmacokinetic or pharmacodynamic mechanisms. The resulting clinical and toxicologic effects may be unpredictable. For example, when phenytoin is given with alcohol the toxicity of alcohol is increased. When phenytoin is combined with theophylline the effects of both are decreased. When given with anticoagulants the anticoagulant effects may be either increased or decreased. The corresponding literature on drug-toxicant or toxicant-toxicant interactions needs development and is expected to be equally complex.

While children in general may be at increased risk for pharmacokinetic/dynamic reasons, subsets of children may be yet more sensitive due to genetic susceptibility. In an elegant set of studies, Perera et al. (1999) have shown that there is significant transplacental transfer of polyaromatic hydrocarbons (PAHs) and environmental tobacco smoke constituents from mother to fetus, that PAH DNA adducts in maternal and newborn white blood cells are increased from environmental exposure, and that the fetus is more sensitive to genetic damage than the mother. Newborns with

a specific restriction fragment length polymorphism (RFLP), CYP 1A1 MspI, had elevated numbers of adducts compared to those without the RFLP (Perera et al., 1999).

In summary, childhood differences that affect metabolism of xenobiotics include:

- Children have increasing maximum oxygen consumption/basal metabolic rate (VO2max/BMR) throughout childhood (ages 7 to14 yr).
- Both Phase I and Phase II enzyme activities are lower in neonates but not universally, e.g., dealkylation, sulfate and glycine conjugation are less affected.
- Blood esterases are lower at birth and rise gradually during the first year (Acetyl cholinesterase (ACh), aryl esterase, pseudocholinesterase).
- Exocrine pancreatic enzymes are lower at birth; amylase is 10% of adult value; trypsin is also low and develops during the first year.
- Albumin and other proteins that bind xenobiotics are found at decreased levels during the newborn period and early infancy.
- Bilirubin and free fatty acids that can compete for protein binding sites are elevated early in life.

4. Excretion

Studies with a large number of drugs have shown that the majority of these agents are more slowly eliminated in neonates and infants than in adults. While this may be partly due to an increased volume of distribution for water-soluble drugs and their metabolites, additional factors may also be involved. At birth, glomerular function is more developed than tubular function and this persists for six months (Guignard et al., 1975; Arant, 1978; Hook and Hewitt, 1977). Tubular secretion is decreased for many drugs in newborns and infants (Besunder et al., 1988). At birth, the glomerular filtration rate (GFR) is two to four mL/min and increases to eight to 20 mL/min in the first few days of life. Adult values of GFR are reached by three to five months of age. Premature infants may have GFRs as low as 0.6 to 0.8 mL/min (Plunkett et al., 1992; Milsap and Jusko, 1994). Early increases in GFR are related to: increases in cardiac output, decreases in peripheral vascular resistance, increases in mean arterial pressure, increased surface area of the kidney for filtration, and increased membrane pore size (Morselli et al., 1980; Plunkett et al., 1992). These age-related changes in renal function lead to decreased body

clearance and prolonged half-lives in neonates and infants for any chemical that is eliminated by the kidney.

Studies in animals have shown that newborn and young animals have less capacity to excrete chemicals into the bile than do adult animals. Klaassen (1972) observed that ouabain, a drug that is primarily excreted in the bile, was seven fold higher in blood concentration of seven-day-old rats than in 39-day-old rats. Ouabain is 40-fold more toxic in newborn than adult rats. Similarly, indocyanine green and sulfobromophthalein and their glucuronides were excreted more slowly in the bile of neonates than in adult rats (Klaassen, 1973). Ballatori and Clarkson (1982) found that the long half-life of methylmercury in neonatal rats was due to their inability to excrete the chemical in the bile, the main elimination route in adults. These findings suggest that deficiencies in the biliary excretion of certain environmental chemicals in infants and young children are likely.

In summary, childhood factors that affect excretion include:

- Lower renal function in neonates and young children with tubular secretion increasing during the first five months of life.
- Slowly developing biliary function despite a larger liver.
- Generally greater intestinal function in children than in adults.

5. Pharmacokinetic Modeling

Pharmacokinetics (PK) is the description of the disposition of a toxicant. Disposition may differ as noted above among infants, children, and adults due to differences in absorption, distribution, metabolism, and excretion. This can be modeled using physiologically-based pharmacokinetic (PBPK) models. PBPK models give predictions of how the body handles a particular chemical. The models address issues of internal body or tissue dosimetry, route to route extrapolation and interspecies extrapolation. To date relatively few published models for various environmental pollutants address infant and child exposure in a systematic fashion. This is parallel to the bulk of toxicity testing in animals, which is usually initiated in young adult animals. It seems clear from the preliminary studies of PBPK modeling that infants in the first year of life are likely to show increased internal dosages for a variety of agents and their metabolites that are probably

related to adverse effects. The following areas should be adequately addressed by PBPK modeling:

- PBPK modeling for human dosimetry should include a series of infant and child anatomical/physiological profiles to address potentially critical developmental stages e.g., newborn, 3, 6, 9 mo, 1-2 years, 2-8 years, 8-16 years for both male and female. (Additional age profiles may be necessary in some cases).
- Biochemical factors for child adjusted PBPK models may need to be scaled from animal or human adult values but values based on the child's metabolism of drugs using similar enzymes should be incorporated if available.
- When appropriate, subpopulations that may be at greater risk from exposure to a given environmental toxicant should also be included in the analysis (e.g., obese children).

C. Pharmacodynamics

Pharmacodynamics (PD) addresses biological responses in tissues or organs not explained by kinetics. Risk assessment currently addresses biological responses in adults (occupational setting) or in mature animals, with the exception of developmental toxicity studies. However, there may be differences in pharmacodynamics as well as pharmacokinetics with age of the animal. Such pharmacodynamic differences can be seen by qualitatively different responses in young and older animals or between children and adults (e.g., for lead or methyl mercury poisoning). Whenever possible, experimental evidence obtained in young animals (or children) should be used to help account for pharmacodynamic differences with age. For example:

- In assessing cancer risks, exposure data involving young animals should be used when available (e.g., vinyl chloride).
- Time to tumor, dose rate and stop exposure data in young animals should also be incorporated into assessments of cancer risk where possible because that may be relevant to differing pharmacodynamics between children and adults that influences response to toxicants.
- The possibility of applying a biological dose-response model (e.g., Two-Stage Clonal Expansion Model) should be explored to evaluate the potential impact of excessive early life

exposures (e.g., dioxin via breast milk) and concomitant pharmacodynamic differences that impact response to carcinogens.

- Toxic endpoints of special concern with respect to childhood exposures because of potentially different toxicodynamics in children and adults include cancer, asthma, endocrine effects, neurotoxicity and neurodevelopmental effects, immunotoxicity, and developmental and reproductive effects resulting from prenatal and postnatal exposures.

D. Conclusions

There are a number of physiological and behavioral factors that influence response to toxicants. These factors differ between children and adults resulting in differences in exposure and response to toxicants present in air, food, water, and soil. Both behavioral and physiological factors influence exposure at each portal of entry. Pharmacokinetic differences between children and adults include factors that influence absorption, distribution, metabolism, and excretion of toxicants. In addition, infants and children may have qualitatively different responses due to different target tissue sensitivities during windows of susceptibility in the developmental process.

References

Adams WC. 1993. Measurement of Breathing Rate and Volume in Routinely Performed Daily Activities. Final Report. Human Performance Laboratory, Physical Education Department, University of California, Davis. Prepared for the California Air Resources Board, Contract No. A033-205, April 1993.

Agnoud M, Yamaguchi N, Lopez R, Luhby AL, and Glass GBJ. 1969. Correlative study of hydrochloric acid, pepsin, and intrinsic factor secretion in newborns and infants. Am. J. Dig. Dis.14:400-414.

Aranda JV, MacLeod SM, Renton KW, and Eade NR. 1974. Hepatic microsomal drug metabolism and electron transport in newborn infants. J. Pediatr. 85:534-542.

Arant BS. 1978. Developmental patterns of renal functional maturation compared in the human neonate. J. Pediatr. 92:705-712.

Avery GB, Randolph JG, and Weaver T. 1966. Gastric acidity in the first day of life. Pediatrics 37:1005-1007.

Ballatori N and Clarkson TW. 1982. Developmental changes in the biliary excretion of methylmercury and glutathione. Science 216:61-63.

Barltrop D. 1996. The prevalence of pica. Amer J Dis Child 112:116-123.

Bates, DV. 1995. The effects of air poilution on children. Environ Health Perspect 103 (Suppl. 6), 49-53.

Bearer C. 1995. How are children different from adults? Environ Health Perspect 103(suppl 6):7-12.

Besunder J, Reed M, Blumer J. 1988. Principles of drug biodisposition in the neonate - a critical evaluation of the pharmacokinetic-pharmacodynamic interface (Part 1). Clinical Pharmacokinetics 14:189-216.

Boyd, E, in Altman and Ditmer (Eds.), Growth, including reproduction and morphological development, Biological Handbooks, Federation of American Societies for Experimental Biology, Washington, 1962, pages 346-348; cited in Documenta Geigy Scientific Tables, Diem K and Lentner C (Eds.), Ciba-Geigy Corporation, Ardsley, New York (1970).

Brodersen R, Friis-Hansen b, and Stern L. 1983. Drug-induced displacement of bilirubin from albumin in the newborn. Dev. Pharmacol. Ther. 6:217-229

Calabrese EJ, Stanek EJ, James RC, Roberts SM. 1997. Soil ingestion: A concern for acute toxicity in children. Environ Health Perspectives 105(12):1354-1358.

CDHS, California Department of Health Services. 2000. California County Asthma Hospitalizations Chart Book. Environmental Health Investigations Branch. August, 2000

CancerChem 2000. Version 3.0. Electronic database of U.S. Public Health Service Publication No. 149, Survey of Compounds Which Have Been Tested for Carcinogenic Activity, covers literature from 1900 to 1998, GMA Industries, Inc.

Carthew P, Edwards RE, Nolan BM, Martin EA, Heydon RT, White IN, Tucker MJ. 2000. Tamoxifen induces endometrial and vaginal cancer in rats in the absence of endometrial hyperplasia. Carcinogenesis 21(4):793-797.

CDC, 1990. Centers for Disease Control. Mercury exposure from interior latex paint- Michigan. *MMWR* 39:125-126.

Chen YC, Guo YL, Hsu CC, Rogan WJ. 1992. Cognitive development of yu-Cheng ("oil disease") children prenatally exposed to heat-degraded PCBs. JAMA 268: 3213-3218.

Clarren SK, Smith DW. 1978. The fetal alcohol syndrome. N Engl J Med 298, 1063-1067.

Cogliano VJ, Hiatt GF, Den A. 1996. Quantitative cancer assessment for vinyl chloride: indications of early-life sensitivity. Toxicology 111(1-3):21-28.

Couse JF, Davis VL, Hanson RB, Jefferson WN, McLachlan JA, Bullock BC, Newbold RR, Korach KS. 1997. Accelerated onset of uterine tumors in transgenic mice with aberrant expression of the estrogen receptor after neonatal exposure to diethylstilbestrol. Mol Carcinogenesis 19:236-242.

Cresteil T. 1998 Onset of xenobiotic metabolism in children: toxicological implications. Food Addit. Contamin. 15 (Suppl.): 45-51.

Dassen W, Brunekreef B, Hoek G, Hofschreuder P, et al. 1986. Decline in children's pulmonary function during an air pollution episode. J. Air Pollut. Control Assn. 36:1223-1227.

Diamond J. 1991. Pearl Harbor and the emperor's physiologists. *Natural History*. Dec. 2-7.

Diwan BA, Anderson LM, Ward JM 1997. Proliferative lesions of oviduct and uterus in CD-1 mice exposed prenatally to tamoxifen. Carcinogenesis 18(10):2009-2014.

Diwan BA, Riggs, CW, Logsdon D, Haines DC, Olivera OA, Rice JM, Yuspa SH, Poirier MC, Anderson LM. 1999. Multiorgan transplacental and neonatal carcinogenicity of 3'-Azido-3'-deoxythymidine in mice. Toxicol Appl Pharmacol 161:82-99.

Dobbing J. Sands J. 1979. The brain growth spurt in various mammalian species. Early Human Development 3, 79-84.

Donald JM, Hooper K, Hopenhayn-Rich C. Reproductive and developmental toxicity of toluene: a review. Environmental Health Perspectives 94:237-244 (1991).

Drew RT, Boorman GA, Haseman JK, McConnell EE, Busey WM, Moore JA. 1983. The effect of age and exposure duration on cancer induction by a known carcinogen in rats, mice, and hamsters. Toxicol Appl Pharmacol 68:120-130.

Dunnill MS. 1962. Postnatal growth of the lung. Thorax 17:329-333.

Dutton GJ. 1978. Developmental aspects of drug conjugation, with special reference to glucuronidation. Ann. Rev. Pharmacol. Toxicol. 18:17-35.

Ecobichon DJ and Stephens DS. 1973. Perinatal development of human blood esterases. Clin. Pharmacol. Ther.14:11-14.

Ershow, A.G., Cantor, K.P. 1989. Total water and tapwater intake in the United States: Population-based estimates of quantities and sources. *National Cancer Institute* order #263-MD-810264.

Fanucchi MV, Wong VJ, Hinds D, Tarkington BK, Van Winkle LS, Evans MJ, Plopper CG. 2000. Repeated episodes of exposure to ozone alters postnatal development of distal conducting airways in infant rhesus monkeys. Am J Respir Crit Care Med 161:A615.

Fanucchi MV, Plopper CG. 1997. Pulmonary developmental responses to toxicants. In: Comprehensive Toxicology, vol 8 (Roth RA, ed). New York:Pergamon, 203-220.

Findlay, JWA. 1983. The distribution of some commonly used drugs in human breast milk. Drug Metab Rev 14:653-684.

Fleishaker JC, Desai N, McNamara PJ. 1987. Factors affecting the milk-to-plasma drug concentration ratio in lactating women:physical interactions with protein and fat. J Pharmaceutical Sci 76:189-193.

Fomon SJ. Trends in infant feeding since 1950. In: Fomon SJ, ed. Nutrition of Normal Infants. St. Louis: Mosby, 1993:15-31.

Friis-Hansen B. 1961. Body water compartments in children: changes during growth and related changes in body composition. Pediatrics 28:169-181.

Friis-Hansen B. 1971. Body composition during growth. In vivo measurements and biochemical data correlated to differential anatomical growth. Pediatrics 47:264-274.

Gebremichael A, Chang AM, Buchpitt AR, Plopper CG, Pinkerton KE. 1995. Postnatal development of cytochrome P450 1A1 and 2B1 in rat lung and liver: Effect of aged and diluted sidestream cigarrette smoke. Toxicol. Appl Pharmacol. 135(2):246-253.

Ginsberg G. 2000. Xenobiotic metabolism and chemical fate from early childhood onward. *Presentation Children's Environmental Health Symposium*. Oakland CA. May 2, 2000.

Gladen BC, Rogan WJ. 1995. DDE and shortened duration of lactation in a northern Mexican town. Am J Public HealthApr;85(4):504-8

Gladen BC, Ragan NB, Rogan WJ. 2000. Pubertal growth and development and prenatal and lactational exposure to polychlorinated biphenyl and dichlorodiphenyl dichloroethene.. J Pediatr Apr;136(4):490-6.

Golub M. 2000. Adolescent health and the environment. Environ. Health Perspect. 108:355-62.

Groot ME, Lekkerkerk MC, Steenbekkers MLA. 1998. Mouthing behavior of young children: an observational study. Wageningen, The Netherlands:Agricultural University Wageningen,.

Guignard JP, Torrado A, Da Cunha O, and Gautier E. 1975. Glomerular filtration rate in the first three weeks of life. J. Pediatr. 87:268-272.

Gulson BL, Jameson CW, Mahaffey KR, Mizon KJ, Patison N, Law AJ, Korsch MJ, Salter MA. 1998. Relationships of lead in breast milk to lead in blood, urine, and diet of the infant and mother. Environ Health Persepectives 106(10):667-674.

Gurunathan S, Robson M, Freeman N, Buckley B, Roy A, Meyer R, et al. 1998. Accumulation of chlorpyrifos on residential surfaces and toys accessible to children. Environ. Health Perspect. 106:9-16.

Hakkola J, Tanaka E, and Pelkonen O. 1998. Developmental expression of cytochrome P450 enzymes in human liver. Pharmacol. Toxicol. 82:209-217.

Hallen IP, Jorhem L, Oskarsson A. 1996. Placental and lactational transfer of lead in rats: a study on the lactational process and effects on offspring. Arch Toxicol. 69: 596-602.

Hardman JG, Gilman AG, Limbird LE. 1996. Goodman and Gilman's The Pharmacological Basis of Therapeutics, ninth edition. McGraw-Hill, pp. 1568-1570.

Hawley JK. 1985. Assessment of health risk from exposure to contaminated soil. Risk Anal. 5:289-302.

Heimann G. 1980. Enteral absorption and bioavailability in children in relation to age. Eur. J. Clin. Pharmacol.18:43-50.

Herngren L, Ehrnebo M, and Boreus LO. 1983. Drug binding to plasma proteins during human pregnancy and in the perinatal period. Studies on cloxacillin and alprenolol. Dev. Pharmacol. Ther. 6:110-124.

Hislop AA, Wiggleswoth JS, Desai R. 1986. Alveolar development in the human fetus and infant. Early Hum Dev 13:1-11.

Holladay SD, Smialowicz RJ. 2000. Development of the murine and human immune system: differential effects of immunotoxicants depend on time of exposure. Environ Health Perspect 108, 463-473.

Hook JB and Hewitt WR. 1977. Development of mechanisms for drug excretion. Am J Med 62:497-506.

Hoover S, Zeise L, Krowech G. 1991. Exposure to environmental contaminants through breast milk: In: The analysis, communication and perception of risk. Garrick BJ, Gekler WC, editors. Advances in Risk Analysis. New York: Plenum Publishing.

Horner PJ, Gage FH. 2000. Regenerating the damaged central nervous system. Nature 407, 963-970.

IARC 1996. International Agency for Reseaerch on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. *Some Pharmaceutical Drugs*. IARC, Lyon, France, Volume 66, pp. 253-365.

Islam MS, and Schlipkoter HW. 1989. Reversible fraction of airway resistance in healthy children of areas with different levels of atmospheric pollutants. Exp. Pathol. 37:1-4.

Ivankovic S. 1979. Teratogenic and carcinogenic effects of some chemicals during perinatal life in rats, Syrian golden hamsters, and minipigs. Natl Cancer Inst Monogr 51:103-115.

Jacobs BL, van Praag, H and Gage, FH. 2000. Depression and the birth and death of brain cells. American Scientist 88, 340-345.

Jacobson JL, Jacobson SW. 1996. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 335:783-789.

Kaye AM, Trainin N. 1966. Urethan carcinogenesis and nucleic acid metabolism: factors influencing lung adenoma induction. Cancer Res 26:2206-2212.

Kai M, Luebeck EG, Moolgavkar SH. 1997. Analysis of the incidence of solid cancer among atomic bomb survivors using a two-stage model of carcinogenesis. Radiat Res 148(4):348-358.

Kavlock RJ, Daston, GP, DeRosa C, Fenner-Crisp P, Gray LE, Kaattari S, et al. 1996. Research needs for the risk assessment of health and environental effects of endocrine disruptors: A report of the U.s. EPA-sponsored workshop. Environ Health Perspect 104:1-20.

Kimmel CA. 2001. 1999. Warkany lecture: Improving the science for predicting risks to children's health. Teratology 63:202-209.

Kissel JC, Richter KY, Fenske RA. 1996. Field measurement of dermal soil loading attributable to various activities: Implications for exposure assessment. Risk Anal. 16:115-125.

Klaassen CD. 1972. Immaturity of the newborn rat's hepatic excretory function for ouabain. J Pharmacol Exp Ther 183:520-526.

Klaassen CD. 1973. Comparison of the toxicity of chemicals in newborn rats to bile duct-ligated and sham-operated rats and mice. Toxicol Appl Pharmacol 24:37-44.

Klaassen CD. 1996. Absorption, distribution, and excretion of toxicants. In Klaassen CD, Andur MO, Doull J, eds. Casarett and Doull's Toxicology:The basic science of poisons. 5th ed. New York:McGraw-Hill: p. 99-101.

Lacroix D, Sonnier M, Moncion A, Cheron G, and Cresteil T. 1997. Expression of CYP3A in the human liver—evidence that the shift between CYP3A7 and CYP3A4 occurs immediately after birth. Eur J Biochem 247:625-634.

Lai ZW, Fiore NC, Hahn PJ, Gasiewicz TA, Silverstone AE. 2000. Differential effects of diethylstilbestrol and 2,3,7,8-tetrachlorodibenzo-p-dioxin on thymocyte differentiation, proliferation, and apoptosis in bcl-2 transgenic mouse fetal thymus organ culture. Toxicol Appl Pharmacol 168:15-24.

Lash TL, Aschengrau A. 1999. Active and passive cigarette smoking and the occurrence of breast cancer. Am J Epidemiol 149:5-12.

Laib RJ, Bolt HM, Cartier R, Bartsch H 1989. Increased alkylation of liver DNA and cell turnover in young versus old rats exposed to vinyl chloride correlates with cancer susceptibility. Toxicol Lett 45(2-3):231-239.

Levy G, Khanna NN, Soda DM, Tsuzuki O, and Stern L. 1975. Pharmacokinetics of acetaminophen in the human neonate: formation of acetaminophen glucuronide and sulfate in relation to plasma bilirubin concentration and *d*-glucaric acid excretion. Pediatrics 55:818-825.

Linet MS, Ries LA, Smith MA, Tarone RE, Devesa SS. 1999. Cancer surveillance series: Recent trens in childhood cancer incidence and mortality in the United States. JNCI 91:1051-1058.

Lonnerdal B. 1994. Nutritional Aspects of Soy Formula. Acta Paediatr Suppl 402:105-8.

Makris S, Raffaele ., Sette W, Seed J. 1998. A Retrospective Analysis of Twelve Developmental Neurotoxicity Studies Submitted to the US EPA Office of Prevention, Pesticides and Toxic Substances (OPPTS). Presentation to the FIFRA Scientific Advisory Panel. December 9, 1998 (November 12, 1998 draft).
http://www.epa.gov/epahome/scipoly/sap/index.htm

Makris S. 2000. The Use of the Developmental Neurotoxicity Study in the Regulation of Pesticides by USEPA: Hot Issues and Fascinating Opportunities. Presentation at the Eighteenth International Neurotoxicology Conference Sept 26, 2000. Colorado Springs.

Maekawa A, Mitsumori K 1990. Spontaneous occurrence and chemical induction of neurogenic tumors in rats – influence of host factors and specificity of chemical structure. Crit Rev Toxicol 20(14):287-310.

Maltoni C, Lefemine G, Ciliberti A, Cotti G, Carretti D 1981. Carcinogenicity Bioassays of Vinyl Chloride Monomer: A model of Risk Assessment on an Experimental Basis. Environ Hlth Perspect 41:3-29.

Marcus PM, Newman B, Millikan RC, Moorman PG, Baird DD, Qaqish B. 2000. The associations of adolescent cigarette smoking, alcoholic beverage consumption, environmental tobacco smoke, and ionizing radiation with subsequent breast cancer risk (United States). Cancer Causes Control 11:271-278.

McFadden SW, Haddow JE. 1969. Coma produced by topical application of isopropanol. Pediatrics 43:622-3.

McKinney PA, Alexander FE, Cartwright RA, Parker L 1991. Parental occupations of children with leukaemia in West Cumbria, North Humberside, and Gateshead. Br Med J 302(6778):681-687.

Mende P, Spiegelhalder B, Preussmann R 1991. Trace analysis of nitrosated foodstuffs for nitrosamides. Food Chem Toxicol 29(3):167-172.

Miller RA. 1941. Observations on the gastric acidity during the first month of life. Arch Dis Child 16:22-30.

Milsap RL, Jusko WJ. 1994. Pharmacokinetics in the infant. Environ. Health Perspect. 102(Suppl 11):107-110.

Morabia A, Bernstein MS, Bouchardy I, Kurtz J, Morris MA. 2000. Breast cancer and active and passive smoking: the role of the N-acetyltransferase 2 genotype. Am J Epidemiol 152:226-232.

Morselli PL. 1976. Clinical pharmacokinetics in neonates. Clin. Pharamcokinet.1:81-98.

Morselli PL, Franco-Morselli R, and Bossi L. 1980. Clinical pharmacokinetics in newborns and infants. Age-related differences and therapeutic implications. Clin Pharmacokinet 5:485-527.

Morselli PL. 1989. Clinical pharmacology of the perinatal period and early infancy. Clin Pharmacokinet 17(Suppl. 1):13-28.

Muller G., Spassovski M., Henschler D. 1972. Trichloroethylene exposure and trichloroethylene metabolites in urine and blood. Arch Toxicol 29:335-340.

Murphy GM. Signer E. 1974. Progress report: bile acid metabolism in infants and children. Gut 15:151-163.

Nagaraja TN, Desiraju T 1994. Effects on operant learning and brain acetylcholine esterase activity in rats following chronic inorganic arsenic intake. Hum Exp Toxicol 13, 353-356.

NCI. 1999. National Cancer Institute. *Health Effects of Exposure to Environmental Tobacco Smoke: The Report of the California Environmental Protection Agency*. Smoking and Tobacco Control Monograph no. 10. Bethesda MD. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, NIH Pub. No. 99-4645.

Needleman HL, Gunnoe C, Leviton A, Reed R, Peresie H, Maher C, and Barrett P. 1979. Deficits in psychologic and classroom performance of children with elevated dentine levels. N Engl J Med 100:689-695.

Neims AH, Warner M, Loughnan PM, and Aranda JV. 1976. Developmental aspects of the hepatic cytrochrome P450 monooxygenase system. Annu Rev Pharmacol Toxicol 16:427-445.

Newbold RR, Hanson RB, Jefferson WN, Bullock BC, Haseman J, McLachlan JA. 1998. Increased tumors but uncompromised fertility in the female descendants of mice exposed developmentally to diethylstilbestrol. Carcinogenesis 19(9):1655-1663.

Newbold RR, Jefferson WN, Padilla-Burgos E, Bullock BC. 1997. Uterine carcinoma in mice treated neonatally with Tamoxifen. Carcinogenesis 18(12):2293-2298.

NRC. 1993. National Research Council. Pesticides in the Diets of Infants and Children. *National Academy Press*. Washington D.C.

NRC.1990a. National Research Council.Recommended Dietary Allowances. 10th Ed. National Academy Press. Washington, D.C.

NRC. 1990b. National Research Council *Health effects of exposure to low levels of ionizing radiation*. BEIR V, Committee on the Biological Effects of Ionizing Radiation. National Academy Press: Washington, D.C.

Office of Environmental Health Hazard Assessment (OEHHA). 1999. *Evidence on the carcinogenicity of estragole*. OEHHA, California Environmental Protection Agency, Oakland, California, November 1999. www.oehha.org/prop65/pdf/estragf.pdf.

Office of Environmental Health Hazard Assessment (OEHHA). 1999a. Air Toxics Hot Spots Program Risk Assessment Guidelines Part I: Technical Support Document for the Determination of Acute Reference Exposure Levels for Airborne Toxicants. Office of Environmental Health Hazard Assessment, Cal/EPA. March, 1999 Available at www.oehha.ca.gov.

Office of Environmental Health Hazard Assessment (OEHHA). 1999b. Air Toxics Hot Spots Program Risk Assessment Guidelines Part II: Technical Support Document for Describing Available Cancer Potency Factors. Office of Environmental Health Hazard Assessment, Cal/EPA. April, 1999. Available at www.oehha.ca.gov

Office of Environmental Health Hazard Assessment (OEHHA). 2000. Air Toxics Hot Spots Program Risk Assessment Guidelines Part IV: Technical Support Document for Exposure Assessment and Stochastic Analysis. Office of Environmental Health Hazard Assessment, Cal/EPA. September 2000. Available at ww.oehha.ca.gov.

Olivera OA, Anderson LM, Diwan BA, Haines C, Harbaugh SW, et al. 1997, Transplacental effects of 3'-azido-3'-dideoxythymidine (AZT): Tumorigenicity in mice and genotoxicity in mice and monkeys. JNCI 89:1602-1609.

Olney JW, Farber NB, Wozniak DF, Jevtovic-Todorovic V, Ikonomidou C. 2000. Environmental agents that have the potential to trigger massive apoptotic neurodegeneration in the developing brain. Environ Health Perspect 108 (suppl3):383-388.

Oskarsson A, Schutz A, Skerfving S, Hallen IP, Ohlin B, Lagerkvist BJ. 1996. Total and inorganic mercury in breast milk and blood in relation to fish consumption and amalgam fillings in lactating women. Arch Environ Health 51:234-241.

Patandin, S, Dagnelie PC, Mulder PG, Op de Coul E, van der Veen JE. Weisglas-Kuperus N, Sauer PJ. 1999. Dietary exposure to polychlorinated biphenyls and dioxins from infancy until adulthood: A comparison between breast-feeding, toddler, and long-term exposure. Environ Health Perspect 107:45-51.

Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, Rapoport JL, Evans AC. 1999. Structural maturation of neural pathways in children and adolescents: In Vivo study. *Science* 283:1908-11.

Perera F, Jedrychowski W, Ranh V, Whyatt RM. 1999. Molecular epidemiologic research on the effects of environmental pollutants on the fetus. Environ.. Health Perspect. 107(S3) 451-460.

Perkins CI, Cohen R, Young JL, Schlag R, Wright WE. 1997. *Cancer in California: detailed site and histology, 1990-1994.* California Department of Health Service, Cancer Surveillance Section, Sacramento, California, December 1997.

Plopper CG, Fanucchi MV. 2000. Do Urban Environmental Pollutants Exacerbate Childhood Lung Diseases? Environ Health Perspect. Jun;108(6):A252-A253.

Plopper CG, Thurlbeck WM. 1994. Growth, Aging, and Adaptation in Textbook of Respiratory Medicine 2nd Edition ed. Murray and Nadel. W. B. Saunders, Philadelphia.

Plunkett LM, Turnbull D, and Rodericks JV. 1992. Differences between adults and children affecting exposure assessment. In. Similarities and Differences Between Children and Adults. Implications For Risk Assessment. Guzelian PS, Henry CJ, and Olin SS. Eds. ILSI Press (Washington, DC) pp 79-94.

Porterfield S. 2000. Thyroidal dysfunction and environmental chemicals – potential impact on brain development. Environ Health Persepct 108:433-438.

Preston-Martin S. 1989. Epidemiological studies of perinatal carcinogenesis. In: Napalkov NP, Rice JM, Tomatis L, Yamasaki H (eds.) *Perinatal and Multigenerational Carcinogenesis*. International Agency for Research on Cancer, Lyon, France.

Rane A, Wilson JT. 1976. Clinical pharmacokinetics in infants and children. Clin Pharmacokinet 1:2-24.

Reed, M. 1996. Principles of Drug Therapy in Nelson's Textbook of Pediatrics 15th Ed. W.B. Saunders, Philadelphia.

Reis LAG, Smith MA, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds.) 1999. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995*, National Cancer Institute, NIH Publication 99-4649. Bethesda, MD.

Renwick AG. 1998. Toxicokinetics in infants and children in relation to the ADI and TDI. Food Addit. Contam. 15:17-35

Renwick AG, Dorne JL, and Walton K. 2000. An analysis of the need for an additional uncertainty factor for infants and children. Regul Toxicol Pharmacol 31:286-296.

Rice D, Barone S. 2000. Critical periods of vulnerability for the developing nervous system: Evidence from humans and animals. Environ Health Perspect 108(suppl3):511-533.

Roberts RJ. 1984. Drug Therapy in Infants: Pharmacologic Principles and Clinical Experience. WB Saunders Co., Philadelphia.

Rodier P. 1994. Vulnerable periods and processes during central nervous system development. Environ Health Perspect 102(suppl 2):121-124.

Rodier P. 1995. Developing brain as a target of toxicity. Environ Health Perspect 103(suppl 6):73-76.

Rodier PM, Ingram JL, Tisdale B, Croog VJ. 1997. Linking etiologies in humans and animal models: studies of autism. Reproductive Toxicology 11, 417-422.

Rogan W. 1995. Environmental poisoning of children–lessons from the past. Environ Health Perspect 103(suppl 6):19-23.

Rogan WJ, Gladen BC, McKinney JD, Cerreras, N. Hardy P. Thullen JD, Tingelstad J, Tully M. 1987. PCBs and DDE in human milk effects on growth, morbidity and duration of lactation. Am J Public Health 77, 1294-1297.

Rogers S. 1951. Age of the host and other factors affecting the production with urethane of pulmonary adenomas in mice. J Exp Med 93:427-449.

Ross Products Division, Abbott Laboratories. 2000. Updated breast-feeding trends. Columbus, OH. Unpublished draft supplied to OEHHA by Ross Products Division, Abbott Laboratories.

Rozman KK, Klaassen CD. 1996. Absorption, Distribution, and Excretion of Toxicants in *Casarett amd Doull'sToxicology 5th ed.* Editor Klaassen CD. McGraw-Hill. New York.

Salmon AG, Zeise L, eds. *Risks of Carcinogenesis from Urethane Exposure*, 1991, CRC Press, Inc., Boca Raton.

Schardein JL. Principles of teratogenesis applicable to drug and chemical exposure. Chemically Induced Birth Defects (Second Edition). Pub. Marcell Decker, Inc. (1993).

Schecter A, Papke O, Lis A, Ball M, Ryan JJ, Olson JR, Li L, Kessler H. 1996. Decrease in milk and blood dioxin levels over two years in a mother nursing twins: estimates of decreased maternal and increased infant dioxin body burden from nursing.
Chemosphere. Feb;32(3):543-9

Siegel M, Lebenthal E, and Krantz B. 1984. Effect of caloric density on gastric emptying in premature infants. J. Pediatr 104:118-122.

Siegner E, Fridrich R. 1975. Gastric emptying in newborns and young infants. Acta Paediatr Scand 64:525-530.

Smiley-Jewell SM, Nishio SJ, Weir A, Plopper CG. 1998. Neonatal Clara cell toxicity by 4-ipomeanol alters bronchiolar organization in adult rabbits. Am J Physiol 274:L485-498.

Smiley-Jewell SM, Liu FJ, Weir A, Plopper CG. 2000. Acute injury to differentiating Clara cells in neonatal rabbits results in age-related failure of bronchiolar epithelial repair. Toxicologic Pathology 28(2):267-76.

Smith AH. 1987. Infant exposure assessment for breast milk dioxins and furans derived from incineration emissions. Risk Analysis 7(3):347-353.

Snodgrass WR. 1992. Physiological and biochemical differences between children and adults as determinants of toxic response to environmental pollutants. In. Similarities and Differences Between Children and Adults. Implications For Risk Assessment. Guzelian PS, Henry CJ, and Olin SS. Eds. ILSI Press (Washington, DC) pp 35-42.

Sonnier M, Cresteil T. 1998. Delayed ontogenesis of CYP1A2 in the human liver. Eur J Biochem 251:893-898.

Sram RJ, Binkova B, Rossner P, Rubes J, Topinka J, Dejmek J (1999). Adverse reproductive outcomes from exposure to environmental mutagens. Mutat Res 428:203-15.

Swenberg JA, Fedtke N, Fishbein L. 1992. Age-related differences in DNA adduct formation and carcinogenesis of vinyl chloride in rats. In: Guzelian PS, Henry CJ, Olin SS (eds.)

Similarities and Differences Between Children and Adults: Implications for Risk Assessment. International Life Sciences Institute (ILSI), ILSI Press, Washington D.C.

Thacker SB, Hoffman DA, Smith J, Steinberg K, and Zack M 1992. Effect of low-level body burdens of lead on the mental development of children: limitations of meta-analysis in a review of longitudinal data. Arch Environ Health 47(5):336-346.

Treluyer JM, Gueret G, Cheron G, Sonnier M, and Cresteil T. 1997. Developmental expression of CYP2C and CYP2C-dependent activities in the human liver: in vivo/in vitro correlation and inducibility. Pharmacogenetics 7:441-452.

Treluyer JM, Jacqz-Aigrain E, Alvarez F, and Cresteil T. 1991. Expression of CYP2D6 in developing liver. Eur J Biochem 202:583-588.

Tyrala EE, Hillman LS, Hillman RE, and Dodson WE. 1977. Clinical pharmacology of hexachlorophene in newborn infants. J Pediatr91:481-486.

U.S. EPA 1992. Dermal Exposure Assessment: Principles and Applications. EPA/600/8-91/0118. Washington, D.C.:Office of Health and Environmental Assessment.

U.S. EPA 1997.Exposure Factors Handbook Volume I-III. EPA/600/P-95/002Fa,b,c. Washington, D.C.:Office of Research and Development,

U.S. EPA. 2000. Strategy for Research on Environmental Risks to Children. EPA/600/R-00/068, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC.

Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in human liver. Hypermethylation control of gene expression during the neonatal period. Eu. J Biochem 238:476-483.

Wiley JA, Robinson JP, Piazza T, Garett K, Cirkensa K, Cheng YT, Martin G. 1991a. Activity Patterns of California Residents. Final Report. Survey Research Center, University of California, Berkeley. Prepared for the California Air Resources Board, Contrate No. A6-177-31.

Wiley JA, Robinson JP, Cheng YT, Piazza T, Stork L, Pladsen K. 1991b. Study of children's activity patterns. Contract number A733-149. Final Report. California Environmental Protection Agency, Air Resources Board.

Wilkins-Haug L, Gabow P. 1991. Toluene Abuse During Pregnancy: Obstetric Complications and Perinatal Outcomes. Obstetrics and Gynecology 77:504-509

Wilson JG. 1977. Current status of teratology. General principles and mechanisms derived from animal studies. In: Handbok of Teratology. Vol 1 General Principles and Etiology. Wilson JG and Fraser FC, eds. Plenum Press, New York pp.47-74.

Wilson JT, Brown RD, Hinson JL, Dailey JW. 1985. Pharmacokinetic pitfalls in the estimation of the breast milk/plasma ration for drugs. Ann Rev Pharmacol Toxicol 25:667-689.

Zartarian VG, Ozhaynak H, Xue J. 2000. Modeling aggregate chlorpyrifos exposure and dose to children. Tenth Annual Meeting of the International Society of Exposure Analysis, Monterey, California. November 24-27, 2000.

Appendix A **Table A – List of Toxic Air Contaminants**
Table B – List of Toxic Air Contaminants that dropped out of the process after the initial ranking

Table A -- All Toxic Air Contaminants

Acetaldehyde
Acetamide
Acetonitrile
Acetophenone
2-Acetylaminofluorene
Acrolein
Acrylamide
Acrylic acid
Acrylonitrile
Allyl chloride
Aluminum and compounds
4-Aminobiphenyl
Ammonia
Ammonium nitrate
Ammonium sulfate
Aniline
Antimony compounds
Arsenic and compounds
Asbestos
Barium compounds
Benzene
Benzidine
Benzo[a]pyrene (PAHs and other POMs)
Benzotrichloride
Benzoyl chloride
Benzyl chloride
Beryllium compounds
beta-Propiolactone
Biphenyl
Bis(2-ethylhexyl) adipate
Bis(2-ethylhexyl)phthalate (DEHP)
Bis(chloromethyl)ether
Bromine compounds (inorganic)
Bromoform
1,3-Butadiene
Butyl acrylate
Butyl benzyl phthalate
Cadmium and compounds
Calcium cyanamide
Caprolactam
Captan
Carbaryl
Carbon black extracts
Carbon disulfide
Carbon tetrachloride

Carbonyl sulfide
Catechol
Chloramben
Chlordane
Chlorinated fluorocarbons
Chlorine
Chlorine dioxide
Chloroacetic acid
2-Chloroacetophenone
Chlorobenzene
Chlorobenzilate
Chloroform
Chloromethyl methyl ether
Chlorophenols
Chloroprene
Chromium compounds (trivalent)
Chromium VI
Cobalt compounds
Coke oven emissions
Copper compounds
Creosotes
Cresols/Cresylic acid (isomers/mixtures)
Crystalline silica
Cumene
Cumene hydroperoxide
Cyanide compounds
Cyclohexane
2,4-D, salts and esters
DDE
Decabromodiphenyl oxide
Dialkylnitrosamines
Diaminotoluene (mixed isomers)
Diazomethane
Dibenzofuran
1,2-Dibromo-3-chloropropane (DBCP)
Dibutylphthalate
1,4-Dichlorobenzene (p-Dichlorobenzene)
3,3'-Dichlorobenzidene
Dichloroethyl ether (Bis(2-chloroethyl)ether)
1,3-Dichloropropene (Telone)
Dichlorvos (DDVP)
Dicofol
Diesel Exhaust PM
Diethanolamine
Diethyl sulfate
Dimethyl aminoazobenzene
3,3'-Dimethyl benzidine
Dimethyl carbamoyl chloride
Dimethyl formamide

1,1-Dimethyl hydrazine
Dimethyl phthalate
Dimethyl sulfate
3,3'-Dimethyoxybenzidine
4,6-Dinitro-o-cresol, and salts
2,4-Dinitrophenol
2,4-Dinitrotoluene
1,4-Dioxane (1,4-Diethyleneoxide)
1,2-Diphenylhydrazine
Epichlorohydrin (1-Chloro-2,3-epoxypropane)
1,2-Epoxybutane
Ethyl acrylate
Ethyl benzene
Ethyl carbamate (Urethane)
Ethyl chloride (Chloroethane)
Ethylene dibromide (Dibromoethane)
Ethylene dichloride (1,2-Dichloroethane)
Ethylene glycol
Ethylene imine (Aziridine)
Ethylene oxide
Ethylene thiourea
Ethylidene dichloride (1,1-Dichloroethane)
Fine Mineral Fibers
Formaldehyde
Gasoline vapors
Glutaraldehyde
Glycol ethers
Heptachlor
Hexachlorobenzene
Hexachlorobutadiene
Hexachlorocyclohexanes
Hexachlorocyclopentadiene
Hexachloroethane
Hexamethylene-1,6-diisocyanate
Hexamethylphosphoramide
Hexane (n-)
Hydrazine
Hydrochloric acid
Hydrogen fluoride (Hydrofluoric acid)
Hydrogen selenide
Hydrogen sulfide
Hydroquinone
Isocyanates (methylene diphenyl diisocyanate & eg TDI)
Isophorone
Isopropyl alcohol
4,4'-Isopropylidenediphenol
Lead and compounds
Lindane (all isomers)
Maleic anhydride

Manganese compounds
Mercury and compounds
Methanol
Methoxychlor
Methyl bromide (Bromomethane)
Methyl chloride (Chloromethane)
Methyl chloroform (1,1,1-Trichloroethane)
Methyl ethyl ketone (2-Butanone)
Methyl hydrazine
Methyl iodide (Iodomethane)
Methyl isobutyl ketone (Hexone)
Methyl isocyanate
Methyl methacrylate
Methyl tert-butyl ether (MTBE)
4,4'-Methylene bis(2-chloroaniline) (MOCA)
Methylene chloride (Dichloromethane)
4,4'-Methylenedianiline
Molybdenum trioxide
N,N-Dimethylaniline
Naphthalene
n-Butyl alcohol
Nickel and compounds
Nitric acid
Nitrilotriacetic acid
Nitrobenzene
4-Nitrobiphenyl
4-Nitrophenol
2-Nitropropane
N-Nitrosodimethylamine
N-Nitrosomorpholine
N-Nitroso-n-methylurea
o-Anisidine
o-Toluidine
Parathion
Pentachloronitrobenzene (Quintobenzene)
Pentachlorophenol
Peracetic acid
Phenol
2-Phenylphenol
Phosgene
Phosphine
Phosphoric acid
Phosphorus
Phthalic anhydride
Polychlorinated biphenyls (PCBs)
p-Phenylenediamine
1,3-Propane sultone
Propene
Propionaldehyde

Propoxur (Baygon)
Propylene dichloride (1,2 Dichloropropane)
Propylene oxide
1,2-Propylenimine (2-Methyl aziridine)
Quinoline
Quinone
Radionuclides (including radon)
sec-Butyl alcohol
Selenium compounds
Silver compounds
Sodium hydroxide
Styrene
Styrene oxide
Sulfuric acid
Terephthalic acid
tert-Butyl alcohol
2,3,78-Tetrachlorodibenzo-p-dioxin (chlorinated dioxins and dibenzofurans)
1,1,2,2-Tetrachloroethane
Tetrachloroethylene (Perchloroethylene)
Thiourea
Titanium tetrachloride
Toluene
2,4-Toluene diisocyanate
2,4-Toluenediamine (2,4-Diaminotoluene)
Toxaphene (chlorinated camphene)
1,2,4-Trichlorobenzene
1,1,2-Trichloroethane (Vinyl trichloride)
Trichloroethylene
2,4,5-Trichlorophenol
2,4,6-Trichlorophenol
Triethylamine
Trifluralin
1,2,4-Trimethylbenzene
2,2,4-Trimethylpentane
Vinyl acetate
Vinyl bromide
Vinyl chloride
Vinylidene chloride (1,1-Dichloroethylene)
Xylenes (isomers and mixtures)
Zinc compounds

Table B – Table of TACs that fell out at the intial stages due to no CRELs, cancer potency factors or inadequate ambient air level data, and no other obvious reason for concern for differential effects from airborne exposure based on known toxicity. N = no data available.

Compound	Ambient Data (ng/m^3)	California Cancer Unit Risk Factor	Acute REL	Chronic REL
Acetamide	N	2×10^{-5}	N	N
Acetonitrile	50	N	N	N
Acetophenone	150	N	N	N
2-Acetylaminofluorene	N	1.3×10^{-3}	N	N
Acrylic acid	N	N	N	N
Allyl chloride	N	6×10^{-6}	N	N
Aluminum and compounds	1400	N	N	N
4-Aminobiphenyl	N	6×10^{-3}	N	N
Ammonium nitrate	N	N	N	N
Ammonium sulfate	N	N	N	N
Antimony compounds	2.8	N	N	N
Barium compounds	31.4	N	N	N
Benzotrichloride	N	N	N	N
Benzoyl chloride	N	N	N	N
Beta-Propiolactone	N	4×10^{-3}	N	N
Biphenyl	N	N	N	N
Bis(2-ethylhexyl) adipate	N	N	N	N
Bis(chloromethyl)ether	N	1.3×10^{-2}	N	N
Bromine compounds (inorganic)	8.4	N	N	N
Bromoform	2300	N	N	N
Butyl acrylate	N	N	N	N
Butyl benzyl phthalate	N	N	N	N
Calcium cyanamide	N	N	N	N
Caprolactam	N	N	N	N
Captan	N	6.7×10^{-7}	N	N
Carbaryl	N	N	N	N
Carbon black extracts	N	N	N	N
Carbonyl sulfide	1200	N	N	N
Catechol	N	N	N	N
Chloramben	N	N	N	N
Chlorinated fluorocarbons	N	N	N	700
Chlorine dioxide	N	N	N	N
Chloroacetic acid	N	N	N	N
2-Chloroacetophenone	N	N	N	N
Chlorobenzilate	N	N	N	N
Chloromethyl methyl ether	N	6.9×10^{-4}	N	N
Chlorophenols	N	N	N	N
Chromium compounds (trivalent)	3.9	N	N	N
Cobalt compounds	8	N	N	N
Coke oven emissions	N	6.2×10^{-4}	N	N
Creosotes	N	N	N	N
Crystalline silica	N	N	N	N

Cumene	N	N	N	N
Cumene hydroperoxide	N	N	N	N
Cyanide compounds	N	N	N	N
Cyclohexane	N	N	N	N
2,4-D, salts and esters	N	N	N	N
Decabromodiphenyl oxide	N	N	N	N
Dialkylnitrosamines	2400	N	N	N
Diaminotoluene (mixed isomers)	N	N	N	N
Diazomethane	N	N	N	N
Dibenzofuran	N	N	N	N
Dibutylphthalate	1300	N	N	N
3,3'-Dichlorobenzidene	N	3.4×10^{-4}	N	N
Dichloroethyl ether (Bis(2-chloroethyl)ether)	N	7.1×10^{-6}	N	N
1,3-Dichloropropene (Telone)	N	1.6×10^{-5}	N	N
Dicofol	N	N	N	N
Diethanolamine	N	N	N	N
Diethyl sulfate	N	N	N	N
Dimethyl aminoazobenzene	N	1.3×10^{-3}	N	N
3,3'-Dimethyl benzidine	N	N	N	N
Dimethyl carbamoyl chloride	N	3.7×10^{-3}	N	N
Dimethyl formamide	9800	N	N	N
1,1-Dimethyl hydrazine	N	4.9×10^{-4}	N	N
Dimethyl phthalate	N	N	N	N
3,3'-Dimethyoxybenzidine	N	N	N	N
4,6-Dinitro-o-cresol, and salts	N	N	N	N
2,4-Dinitrophenol	N	N	N	N
2,4-Dinitrotoluene	N	8.9×10^{-5}	N	N
1,2-Diphenylhydrazine	N	N	N	N
1,2-Epoxybutane	N	N	N	N
Ethyl benzene	1610	N	N	N
Ethyl carbamate (Urethane)	N	2.9×10^{-4}	N	N
Ethylene glycol	N	N	N	N
Ethylene imine (Aziridine)	N	1.9×10^{-2}	N	N
Ethylene thiourea	N	1.3×10^{-5}	N	N
Fine Mineral Fibers	N	N	N	N
Hexachlorobutadiene	N	N	N	N
Hexamethylene-1,6-diisocyanate	N	N	N	N
Hexamethylphosphoramide	N	N	N	N
Hydroquinone	N	N	N	N
Isophorone	N	N	N	N
Isopropyl alcohol	N	N	N	N
4,4'-Isopropylidenediphenol	N	N	N	N
Methoxychlor	0.1	N	N	N
Methyl chloride (Chloromethane)	1550	N	N	N
Methyl hydrazine	N	N	N	N
Methyl iodide ((Iodomethane)	55.9	N	N	N
Methyl isobutyl ketone (Hexone)	N	N	N	N
Methyl tert-butyl ether (MTBE)	N	N	N	N

4,4'-Methylene bis(2-chloroaniline) (MOCA)	N	4.3×10^{-4}	N	N
Molybdenum trioxide	N	N	N	N
N,N-Dimethylaniline	N	N	N	N
n-Butyl alcohol	N	N	N	N
Nitric acid	N	N	N	N
Nitrilotriacetic acid	N	1.5×10^{-6}	N	N
4-Nitrobiphenyl	6	N	N	N
4-Nitrophenol	N	N	N	N
N-Nitrosomorpholine	N	1.9×10^{-3}	N	N
N-Nitroso-n-methylurea	N	3.4×10^{-2}	N	N
o-Anisidine	N	4×10^{-5}	N	N
o-Toluidine	N	5.1×10^{-5}	N	N
Parathion	N	N	N	N
Pentachloronitrobenzene (Quintobenzene)	N	N	N	N
Peracetic acid	N	N	N	N
2-Phenylphenol	N	N	N	N
Phosgene	N	N	12	N
Phosphoric acid	N	N	N	N
Phosphorus		N	N	N
p-Phenylenediamine	N	N	N	N
1,3-Propane sultone	N	6.9×10^{-4}	N	N
Propene	N	N	N	N
Propionaldehyde	10,000	N	N	N
Propoxur (Baygon)	2.5	N	N	N
1,2-Propylenimine (2-Methyl aziridine)	N	N	N	N
Quinoline	340	N	N	N
Quinone	N	N	N	N
Radionuclides (including radon)	N	N	N	N
Sec-Butyl alcohol	N	N	N	N
Silver compounds	N	N	N	N
Styrene oxide	N	4.6×10^{-5}	N	N
Sulfuric acid	N	N	N	N
Terephthalic acid	N	N	N	N
tert-Butyl alcohol	N	N	N	N
Thiourea	N	2.1×10^{-5}	N	N
Titanium tetrachloride	N	N	N	N
2,4-Toluenediamine (2,4-Diaminotoluene)	N	1.1×10^{-3}	N	N
Toxaphene (chlorinated camphene)	N	3.4×10^{-4}	N	N
1,2,4-Trichlorobenzene	1300	N	N	N
2,4,5-Trichlorophenol	200	N	N	N
Triethylamine	3400	N	N	N
Trifluralin	0.27	N	N	N
1,2,4-Trimethylbenzene	N	N	N	N
2,2,4-Trimethylpentane	2200	N	N	N
Vinyl acetate	N	N	N	N
Vinyl bromide	N	N	N	N